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(57) Abstract

Methods and matrices are provided for purifying a desired target oligonucleotide using an immobilized affinity unit that selectively binds the target oligonucleotide. The immobilized affinity unit preferably comprises a nucleobase sequence which comprises the reverse complement of the target oligonucleotide. Preferred methods of the invention result in the rapid, cost-effective and efficacious separation of most undesired contaminants, particularly undesired deletion [e.g., (n-1), (n-2), etc.] derivatives of the desired full length (n) oligonucleotide that result from incomplete oligomerization or through degradative processes, including those undesired derivatives having internal or 3' deletions of one or more nucleotides.

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LARGE-SCALE PURIFICATION OF FULL LENGTH OLIGONUCLEOTIDES BY SOLID-LIQUID AFFINITY EXTRACTION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of Serial No. 08/769,951 filed December 19, 1996.

FIELD OF THE INVENTION

This invention relates to methods for purifying a desired full length synthetic oligonucleotide (the target oligonucleotide) from a mixture containing undesired contaminants (e.g., deletion derivatives of the target oligonucleotide) using an immobilized affinity unit that selectively and reversibly binds the target oligonucleotide. Under appropriately stringent conditions, hybridization between the target oligonucleotide and the affinity unit, which comprises a nucleobase sequence having reverse complementary to the nucleobase sequence of at least a central portion of the target oligonucleotide, results in the selective retention of the desired full length (n) target oligonucleotide. Undesired derivatives (e.g., all forms of (n-1), (n-2), etc.) of the target oligonucleotide that result from, e.g., incomplete oligomerization during synthesis or degradative processes either fail to hybridize, and are not so retained, or hybridize with a lesser affinity

than the target oligonucleotide and may thus be removed by treatments (e.g., changes in pH, ionic strength, temperature, and the like) which do not significantly effect the hybridization between the affinity unit and the target oligonucleotide. The desired full length (n) target oligonucleotide is thus rapidly, cost-effectively and efficaciously separated from undesired contaminants including the undesired derivatives (e.g., all forms of (n-1), (n-2), etc.) of the target oligonucleotide that result from, e.g., incomplete oligomerization during synthesis or degradative processes. Preferred matrices for practicing the methods of the invention are also herein provided.

BACKGROUND OF THE INVENTION

During chemical oligonucleotide synthesis, a series of nucleoside monomers are sequentially attached to each other in a predetermined order so that an oligonucleotide having a desired sequence is obtained. Each nucleoside monomer is attached to the growing chain sequentially through a series of chemical reactions or "steps." For example, a process of oligonucleotide synthesis generally comprises the steps of (1) blocking chemically reactive sites on the base portion of a first and second selected nucleoside with unreactive "blocking groups," (2) coupling the first selected base-blocked nucleoside monomer to an inorganic support via a 3' hydroxyl linkage from the pentose portion of the first nucleoside monomer, (3) "protecting" the 5' hydroxyl position of the pentose portion of the second selected base-blocked nucleoside monomer, for example, by chemically attaching a dimethoxytrityl (DMTr) group thereto, (4) attaching the second selected base- and 5'-blocked nucleoside monomer via a linkage spanning the 5' carbon of the pentose portion of the first selected base-blocked nucleoside monomer and the 3' carbon of the pentose portion of the second selected base- and 5'-blocked nucleoside monomer, (5) acylating or otherwise "capping" unreacted nucleoside monomers and (6)

"deprotecting" (e.g., detrityling) the linked nucleosides, i.e., removing the DMTr or other protecting group attached to the 5' hydroxyl position of the pentose portion of the second selected base-blocked nucleoside monomer in order to regenerate a reactive site for a second cycle of such steps. Upon completion of a desired number of such cycles, the oligonucleotide is "deblocked" (i.e., the blocking groups attached to the bases of the oligonucleotide are removed) and a desired biological activity is then realized.

Such methods of oligonucleotide synthesis include, for example, those commonly known as the "phosphite triester method," the "phosphotriester method" and the "H-phosphonate method." Methods for the solution phase synthesis of oligonucleotides have also been described (see U.S. Patent No. 5,210,264 to Yau, assigned to the present applicants; Reese *et al.*, *J. Chem. Soc. Perkin Trans.*, 1993, *1*, 2291; and Wada *et al.*, *Tetrahedron*, 1993, *49*, 2043). Regardless of which method is used, however, the stepwise yield for each nucleoside addition is typically about 99%. Thus, approximately 1% of the oligomers fail nucleoside monomer addition in each step. Such failures of addition result from incomplete coupling, incomplete capping, incomplete detritylation, undesired retritylation through oxidation or by other mechanisms. For a desired synthetic oligonucleotide product of length n, the resulting oligonucleotides are, e.g., one oligonucleotide (n-1), two oligonucleotides (n-2), etc. shorter in length than the desired oligonucleotide and are present as undesired impurities. Such shorter, undesired oligonucleotides are commonly and collectively referred to as "deletion sequences" or "failure" or "failed" sequences.

At one time, it was believed in the art that the majority of the failed sequences resulted from the "deletion" (or lack of incorporation) of nucleotides present at the 5' end of the desired oligonucleotide. See, for example, U.S. Patent No. 5,352,578 to Agrawal *et al.*, which issued October 4, 1994 (column 1, lines 56-59). However,

Temsamani *et al.* (*Nucl. Acids Res.*, 1995, *23*, 1841) describe experiments in which the sequence identities of (n-1) [and some (n-2) and (n-3)] derivatives of a target full length (n=25 nucleotides) oligonucleotide were determined. Two significant results emerged from these experiments. First, the (n-1) population of sequences was heterogeneous. The second finding, described as a "surprising result," was that there was a high frequency of sequences truncated at the 3' terminus and no deletions within the four most 5' terminal nucleotides. Thus, a need exists for a method of purifying a desired full length synthetic oligonucleotide from a heterogeneous mixture containing "failed" sequence oligonucleotides, wherein deletions (failures of incorporation) are randomly distributed over the entire nucleobase sequence of the target oligonucleotide.

High Pressure Liquid Chromatography (HPLC), reverse-phase chromatography and ion-exchange chromatography are examples of commonly used traditional techniques for the purification of crude synthetic oligonucleotides (Warren *et al.*, Chapter 9 *In: Methods in Molecular Biology, Vol. 26: Protocols for Oligonucleotide Conjugates*, Agrawal, S., Ed., 1994, Humana Press Inc., Totowa, NJ, pages 233-264). However, due to the lack of chromatographic selectivity and product yield, the (n-1)-mer impurities are still present in the full-length (i.e., n-mer) oligonucleotide product after the purification unless a very low yield of desired n-mer is acceptable. It is also known in the art to purify oligonucleotides by denaturing polyacrylamide gel electrophoresis (PAGE), but such methods are not applicable to the mass production of oligonucleotides as the yields obtained by such methods are typically less than 50%. (Ausubel *et al.*, eds., *Short Protocols in Molecular Biology*, 2nd Ed., Greene Publishing Associates and John Wiley & Sons, New York, 1992, p. 2-37).

The present invention provides new methods for the large-scale purification of oligonucleotide substances with superior selectivity and product yield, by solid-liquid

affinity extraction using immobilized affinity units that preferentially bind the desired full length oligonucleotide. The affinity unit comprises an immobilized nucleobase sequence having reverse complementarity to the desired target oligonucleotide over a central portion thereof, the essentially full-length (p, as defined herein) thereof, or the full-length (n) thereof. The method of the invention allows for the purification of a desired full length synthetic oligonucleotide from a mixture of heterogeneous failed sequence oligonucleotides.

Reese (*Tetrahedron*, 1978, *34*, 3143) describes methods for synthesizing nucleoside building blocks for oligonucleotides and early attempts to achieve significant amounts of oligonucleotide synthesis using the phosphotriester method.

U.S. Patent No. 4,458,066 to Caruthers *et al.* (issued July 3, 1984) describe a modification of the phosphite triester method for synthesizing oligonucleotides using nucleotide intermediates bound to inorganic polymer supports.

Caruthers (*Science*, 1985, *230*, 281) describes the phosphite triester method of oligonucleotide synthesis and at least partially automated machines for carrying out this method.

Uhlmann *et al.* (*Chem. Reviews*, 1990, *90*, 543) review the then-prevailing state of the art of synthesis of unmodified and modified oligonucleotides.

Gilham (*J. Am. Chem. Soc.*, 1964, *86*, 4982) describes the synthesis of oligo(dT) and its covalent attachment to cellulose. A method of separating oligomers of adenylic acid using a column of this material is also described.

Seliger *et al.* (*Tetrahedron Letts.*, 1978, *24*, 2115) describe a method of oligonucleotide synthesis in which the last residue incorporated into the desired n-mer is an affinity blocking group. Because the desired full-length (n) oligonucleotide includes the terminal affinity

blocking group, it can be separated from the undesired (i.e., (n-1), (n-2), etc.) products. In many instances, however, it is undesirable to retain the terminal affinity blocking group due to its effect on, e.g., biological activity, and removing the terminal affinity group would be expected to decrease the yield of desired product.

Yashima *et al.* (*J. Chromatography*, 1992, *603*, 111) describe the separation of nucleosides and nucleotide dimers via the use of affinity chromatography on silica gel columns comprising immobilized nucleic acid analogs. Although oligonucleotides are also separable by the method of Yashima *et al.*, it is noted that the resolving power of the system decreases as the target oligonucleotide length increases.

Temsamani *et al.* (*Nucl. Acids Res.*, 1995, *23*, 1841) describe experiments in which the seqence identities of (n-1) [and some (n-2) and (n-3)] derivatives of a target full length oligonucleotide were determined. These experiments demonstrate the distribution of deleted nucleotides in failed sequences is greatest at the 3' terminus of the target oligonucleotide.

International Publication No. WO 90/09393, published August 23, 1990, discloses a method of purifying full length target oligonucleotides from a mixture containing truncated sequences. The method, which depends on hybridization between the 5' end of the target oligonucleotide and a short complementary oligonucleotide that is covalently bound to a solid support, does not distinguish between the target full length oligonucleotide and undesired oligonucleotides having a deletion of one or more internal or 3' nucleotides (see also corresponding U.S. Patents No. 5,352,578 and No. 5,559,221, which issued October 4, 1994 and September 24, 1996, respectively).

International Publication No. WO 96/22299, published July 25, 1996, discloses a method of purifying synthetic oligonucleotides from a sample containing the desired oligonucleotide and failed sequences. The disclosed method uses an anion exchange adsorbent that binds the

desired oligonucleotide in its protected form under conditions of high as well as low ionic strength. In some instances, additional ion exchange steps are required in order to separate the desired full length oligonucleotide from shorter forms (page 6, lines 15-19).

To date, there is no known method for the large-scale purification of an oligonucleotide of length n that provides for the effective and cost-efficient separation of all forms of undesired deletion derivatives from the desired full-length oligonucleotide. Consequently, there remains a need for compositions and methods that can be used to effectively purify a desired full length synthetic oligonucleotide from a heterogeneous mixture containing failed sequence oligonucleotides on a industrial scale in a rapid and cost-effective manner.

SUMMARY OF THE INVENTION

In accordance with the present invention, methods and matrices are provided for the rapid, cost-effective and efficacious removal of undesired derivatives of a desired target oligonucleotide. More particularly, the invention provides methods and matrices for the removal of all forms of undesired deletion derivatives [i.e., (n-1), (n-2), etc.] of the desired full length (n) oligonucleotide, including those undesired derivatives having an internal or 3' deletion of one or more oligonucleotides. A desired level of large-scale purification of the desired oligonucleotide is achieved according to the methods and matrices of the invention. Such purification is achieved via the use of a matrix comprising an immobilized affinity unit. In one embodiment, the affinity unit comprises a nucleobase sequence having a sequence that is the reverse complement of the target oligonucleotide over a central portion thereof, the essentially full-length (p, as defined herein) thereof, or the full-length (n) thereof. A mixture comprising the desired target oligonucleotide is contacted with a matrix of the invention comprising the immobilized affinity unit under

stringent hybridization conditions, i.e., conditions under which the hybridization (binding) of the desired target oligonucleotide is preferentially achieved. The undesired [e.g., (n-1), (n-2), etc.] derivatives of the target oligonucleotide hybridize poorly, or not at all, to the matrix of the invention under these conditions and are separated by relatively simple techniques (e.g., washing, centrifugation, etc.). Alternatively, the hybridization reaction occurs under conditions wherein some undesired derivatives of the target oligonucleotide are initially bound but are subsequently removed by a first chemical or physical treatment (e.g., changes in pH, ionic strength, temperature, and the like) which result in a change in the environment of the mixture. Following separation of the undesired derivatives of the target oligonucleotide, the bound target oligonucleotide is eluted from the affinity unit by application of a second chemical or physical treatment. The affinity unit remains immobilized to the matrix of the invention and, in a preferred embodiment, is reused for purifying further batches of the desired target oligonucleotide.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying figures and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the modification of a primary amine, attached to a support (indicated by the open circle) by a linker (indicated by $(CH_2)_n$), by 1,4-phenylene diisthiocyanate to form a modified support having a phenylisothiocyanate group.

Figure 2 shows the reaction of the primary amine group of a probe (i.e., affinity unit and spacer) with the isothiocyanate group of the modified support to form a thiocarbamyl adduct, thereby covalently attaching the probe portion to the support via the linker.

Figure 3 shows an electropherogram of crude ISIS 2302.

Figure 4 shows an electropherogram of ISIS 2302 prepared by a method of the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed to methods for purifying a desired, full length oligonucleotide by the rapid, cost-effective and efficacious removal of contaminants, including but not limited to undesired deletion (e.g., n-1, n-2, etc.) derivatives of the desired (target) oligonucleotide. This is accomplished via solid-liquid extraction of the oligonucleotide through selective hybridization to an affinity unit that specifically binds the desired oligonucleotide. Matrices comprising such affinity units, useful for practicing the methods of the invention, are also herein provided. Although deletion derivatives of the desired target oligonucleotide are contaminants of particular concern, it will be appreciated by those skilled in the art that other contaminants can be removed by the method of the invention as well. For example, a significant portion of undesired salts can be removed using the method of the invention.

The target oligonucleotides that are purified by the methods and matrices of the invention include, in particular, those intended for uses requiring a relatively low concentration of undesired or uncharacterized contaminants. In particular, the invention is drawn to the purification of target oligonucleotides, particularly antisense oligonucleotides, intended for therapeutic delivery to an animal, including a human. Certain preferred embodiments of the present invention are drawn to the purification of target oligonucleotides designed to have therapeutic activity in an animal, such as a human; such target oligonucleotides may be formulated into a pharmaceutical composition. By "designed to have therapeutic activity," it is meant that the target

oligonucleotide is designed to function in a manner that is prophylactic, palliative or curative with regard to (1) a disorder caused by a hyperproliferation of cells (e.g., cancer), a pathogen (e.g., malaria, AIDS), or from causes that appear to relate to neither pathogens nor hyperproliferative cells (e.g., Alzheimer's disease) or (2) the symptoms of such a disorder. The invention is also drawn to the purification of target oligonucleotides that modulate the expression of a cellular protein, including cell surface proteins. In the context of this invention, "designed to modulate" means designed to either effect an increase (stimulate) or a decrease (inhibit) in the expression of a gene. Such modulation can be achieved by a variety of mechanisms known in the art, including but not limited to transcriptional arrest; effects on RNA processing (capping, polyadenylation and splicing) and transportation; enhancement of cellular degradation of the target nucleic acid; and translational arrest (Crooke, S.T., *et al.*, *Exp. Opin. Ther. Patents*, 1996, *6*, 1). The following tables list, as exemplars, some preferred target oligonucleotides that may be purified according to the methods and matrices of the invention, and the full-length embodiments of their corresponding affinity units. Such desired target oligonucleotides include, but are not limited to, those designed to modulate the expression of cellular surface proteins (Table 1), and those designed to have therapeutic activity against disorders associated with cellular hyperproliferation (Table 2) or having no apparent pathological or hyperproliferative-related cause (Table 3) and diseases resulting from eukaryotic pathogens (Table 4), retroviruses such as human immunodeficency virus (HIV; Table 5) or viral pathogens other than retroviruses (Table 6).

TABLE 1: TARGET OLIGONUCLEOTIDES DESIGNED TO MODULATE CELL SURFACE PROTEINS AND AFFINITY UNITS THEREFOR

Cell Surface Protein	Commercial/ Common Name (if any)	Target Oligonucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
ICAM-1	ISIS 2302	1	2
MDR		106,108,110,112	107,109,111,113

TABLE 2: TARGET OLIGONUCLEOTIDES DESIGNED TO HAVE THERAPEUTIC ACTIVITY AGAINST HYPERPROLIFERATIVE CELLS AND AFFINITY UNITS THEREFOR

Molecular Target	Commercial / Common Name (if any)	Target Oligo-nucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
c-myb	MYB-AS	16	17
DNA methyl transferase		18,20	19,21
vascular endothelial growth factor (VEGF)		22,26,28,30,32,34,36,38,40,42	23,27,29,31,33,35,37,39,41,43
VEGF	Vm	24	25
bcl-2		44,46,48,50,52,54,56,58,60,62,64,66	45,47,49,51,53,55,57,59,61,63,65,67
bcl-2	BCL-2	68	69
bcl-abl		76	77
PKC-Z		70	71
PKC-α	ISIS 3521	72	73
c-raf	ISIS 5132	74	75

TABLE 3: TARGET OLIGONUCLEOTIDES DESIGNED TO HAVE THERAPEUTIC ACTIVITY AGAINST NON-PATHOGENIC AND NON-HYPERPROLIFERATIVE DISORDERS, AND AFFINITY UNITS THEREFOR

Disorder	Commercial/ Common Name (if any)	Target Oligo-nucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
Alzheimer's disease		78,80,82,84,86,88, 90,92,94,96,98,100	79,81,83,85,87,89,91,93,95,97,99,101
Beta-thalassemia	5'ss & 3'ss	102 & 104	103 & 105

TABLE 4: TARGET OLIGONUCLEOTIDES DESIGNED TO HAVE THERAPEUTIC ACTIVITY AGAINST EUKARYOTIC PATHOGENS AND AFFINITY UNITS THEREFOR

Pathogen / Disease	Commercial/ Common Name (if any)	Target Oligo-nucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
Plasmodium / malaria		114,116,118,120	115,117,119,121
Schistosoma / bloodfluke infections		122	123

TABLE 5: TARGET OLIGONUCLEOTIDES DESIGNED TO HAVE THERAPEUTIC ACTIVITY AGAINST RETROVIRUSES, INCLUDING HIV, AND AFFINITY UNITS THEREFOR

Virus / Molecular Target	Commercial/ Common Name (if any)	Target Oligo-nucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
HTLV-III / primer binding site		124,126,128,130, 132,134	125,127,129,131, 133,135
HIV-1 / *gag*	GEM-91	136	137
HIV-1 / *gag*	GEM-92, GEM-93	138,140,142,144,146, 148,150,152,154	139,141,143,145,147,149,151, 153,155
HIV	AR 177	156	157
HIV / *tat, vpr, rev, env, nef*		158,160,162	159,161,163
HIV / *pol, env, vir*		164,166,168,170, 172,174,176,178	165,167,169,171, 173,175,177,179
HIV-1 / *tat, rev, env, nef*		180,181;183,184; 186;188	182;185;187;189
HIV / *gp120*	ISIS 5320	190	191

TABLE 6: TARGET OLIGONUCLEOTIDES DESIGNED TO HAVE THERAPEUTIC ACTIVITY AGAINST NON-RETROVIRAL VIRUSES AND AFFINITY UNITS THEREFOR

Virus / Molecular Target	Commercial/ Common Name (if any)	Target Oligo-nucleotide Seq. SEQ ID NO(S):	Affinity Unit Nucleobase Seq. SEQ ID NO(S):
influenza virus		192,194,196,198,200, 202,204,206,208	193,195,197,199,201, 203,205,207,209
Epstein-Barr Virus		228,230,232	229,231,233
Respiratory Syncytial Virus		234,236,238,240	235,237,239,241
cytomegalovirus (CMV)		212,214,216,218, 220,222,224,226	213,215,217,219, 221,223,225,227
CMV	GEM-132	210	211
CMV	ISIS 2922	242	243

Target oligonucleotides that may be purified according to the methods and matrices of the invention include those consisting of naturally occurring nucleotides as well as those comprising one or more chemical modifications. Specific examples of some modified oligonucleotides that can be incorporated into the target oligonucleotide include those containing phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl, cycloalkyl, heteroatomic or heterocyclic intersugar linkages. Specifically, such oligonucleotides include those having phosphorothioates intersugar linkages, those with heteroatomic intersugar linkages including CH_2-NH-O-CH_2, CH_2-$N(CH_3)$-O-CH_2 [known as a methylene(methylimino) or MMI backbone], CH_2-O-$N(CH_3)$-CH_2, CH_2-$N(CH_3)$-$N(CH_3)$-CH_2 and O-$N(CH_3)$-CH_2-CH_2 backbones, wherein the native phosphodiester backbone

is represented as O-P-O-CH_2), thoses with heterocyclic linkages including the morpholino sugar-backbone structures (Summerton and Weller, U.S. No. Patent 5,034,506) or those with a peptide nucleic acid (PNA) backbone (in which the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone wherein the nucleobases is bound directly or indirectly to an aza nitrogen atoms of the polyamide backbone (Nielsen *et al.*, *Science*, 1991, *254*, 1497). Specific examples of modified oligonucleotides also include oligonucleotides containing one or more substituted sugar moieties [i.e., sugar moieties comprising one of the following at the 2' position: -F; -Cl; -Br; -OH; -SH; -SCH_3; -OCN; -OCH_2OCH_3, -$O(CH_2)_nO(CH2)_mCH_3$ (i.e, alkoxyalkoxy), -$O(CH_2)_nNH_2$ or -$O(CH_2)_nCH_3$ where m is from 0 to about 6 and n is from 1 to about 10; C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl or aralkyl; -CN; -CF_3; -OCF_3; O-, S-, or N-alkyl or substituted alkyl; O-, S-, or N-alkenyl; -$SOCH_3$; -SO_2CH_3; -ONO_2; -NO_2; -N_3; -NH_2; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties]. Particularly preferred embodiments include 2'-alkoxyalkoxy substituents such as 2'-*O*-methoxyethoxy [2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl)] (Martin *et al.*, *Helv. Chim. Acta*, 1995, *78*, 486), 2'-methoxy (2'-O-CH_3), 2'-propoxy (2'-$OCH_2CH_2CH_3$) and 2'-fluoro (2'-F). Additional modified oligonucleotides include those having similar modifications at other positions on the oligonucleotide (particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide), oligonucleotides having sugar mimetics such as cyclobutyls in place of the pentofuranosyl group or base modifications or substitutions

(e.g., with a "universal" base such as inosine).

A further modification of the target oligonucleotide involves chemically linking to the target oligonucleotide one or more lipophilic moieties which enhance the cellular uptake of the oligonucleotide. Such lipophilic moieties include but are not limited to a cholesteryl moiety (Letsinger *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1989, *86*, 6553), cholic acid (Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1994, *4*, 1053), a thioether, e.g., hexyl-*S*-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306; Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1993, *3*, 2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, *20*, 533), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, *10*, 111; Kabanov *et al.*, *FEBS Letts.*, 1990, *259*, 327; Svinarchuk *et al.*, *Biochimie*, 1993, *75*, 49), a phospholipid, e.g., di-hexadecyl-*rac*-glycerol or triethylammonium 1,2-di-O-hexadecyl-*rac*-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, *36*, 3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, *18*, 3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, *14*, 969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, *36*, 3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, *1264*, 229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, *277*, 923). Oligonucleotides comprising lipophilic moieties, and methods for preparing such oligonucleotides, are disclosed in U.S. Patents No. 5,138,045, No. 5,218,105 and No. 5,459,255.

The target oligonucleotide can also be an oligonucleotide which is a chimeric oligonucleotide including a "gapmer" or a "hemimer." Chimeric oligonucleotides are oligonucleotides which contain two or

more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one terminal region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the intracellular target nucleic acid. In a "hemimer," a single terminal (either 5' or 3') region is so modified in the oligonucleotide structure. When both termini of the oligonucleotide are modified, the oligonucleotide is called a Agapmer@ and the modified 5'- and 3'-terminal regions are referred to as "wings"; an additional, typically central, region (typically referred to as the "gap" or "core") of the oligonucleotide may serve as a substrate for cellular enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. In a gapmer, the 5' and 3' wings can be modified in the same or different manner depending on what properties it is desired to achieve.

The length of a target oligonucleotide is defined as "n" nucleobases, wherein "n" is a positive whole number. The length of target oligonucleotides that can be purified according to the methods and matrices of the invention is one having from 5 to about 60 nucleobases, preferably from 7 to about 50 nucleobases, more preferably from 8 to about 40 nucleobases, even more preferably from 9 to about 30 nucleobases and most preferably from 10 to about 25 nucleobases. The method of synthesis of the target oligonucleotide does not typically effect the methods of the invention; in general, any method of synthesis, including methods for the solution phase synthesis of oligonucleotides (see U.S. Patent No. 5,210,264 to Yau, assigned to the present applicants; Reese *et al.*, *J. Chem. Soc. Perkin Trans.*, 1993, *1*, 2291; and Wada *et al.*, *Tetrahedron*, 1993, *49*, 2043) may be used.

The matrices of the invention comprise a plurality of a molecular composition that comprises several parts: (1)

a support, (2) an optional linker to the support, (3) an optional spacer and (4) a unit having a high degree of specific affinity to the target oligonucleotide (affinity unit). When present, the linker (2) and spacer (3) provide a bridge between the support (1) and the affinity unit (4) in such a way as to not significantly alter or reduce the binding capacity of the latter element. The probe of the matrix of the invention comprises parts (4) and, optionally, (3). The following paragraphs describe the matrices of the invention in more detail.

With regard to the support (1), a variety of substances may be used. A suitable support has preferred characteristics of non-reactivity with compounds introduced during the various steps of oligonucleotide synthesis, accessibility to solvents utilized during such syntheses, and a tendency towards minimal barrier layer diffusion. A barrier layer is created by an ordering of solvent molecules on the surface of a solid phase support. As this barrier layer is composed of ordered molecules, it is difficult to get consistent reagent diffusion across such a barrier to the molecules of interest which are attached to the support. It will be appreciated by those skilled in the art that the chemical composition of the affinity unit (4), the optional linker (2) and/or the optional spacer (3) may influence the choice of the support (1). The support may be insoluble ("solid") or soluble. The chemical nature of various solid supports, and their desirable properties, are reviewed by Winter (Chapter 17 *In: Combinatorial Peptide and Nonpeptide Libraries: A Handbook*, Jung, ed., VCH Publishers, Inc., New York, NY, 1996, pp. 465-510). Suitable solid supports include, but are not limited to, graft polymers (U.S. Patent No. 4,908,405 to Bayer and Rapp); polyacrylamide (Pahy *et al.*, *Nucl. Acids Res.*, 1993, *21*, 1819); polyacrylmorpholide, polystyrene and derivatized polystyrene resins (Syvanen *et al.*, *Nucl. Acids Res.*, 1988, *16*, 11327; U.S. Patent Nos. 4,373,071 and 4,401,796 to Itakura), including amino methyl styrene resins (U.S. Patent No. 4,507,433 to Miller and

Ts'O); copolymers of N-vinylpyrrolidone and vinylacetate (Seliger *et al.*, *Tetrahedron Letts.*, 1973, *31*, 2911; Seliger *et al.*, *Die Makromolekulare Chemie*, 1975, *176*, 609; and Seliger, *Die Makromolekulare Chemie*, 1975, *176*, 1611); TEFLON™ (Lohrmann *et al.*, *DNA*, 1984, *3*, 122; Duncan *et al.*, *Anal. Biochem.*, 1988, *169*, 104); controlled pore glass (Chow *et al.*, *Anal. Biochem.*, 1988, *175*, 63); polysaccharide supports such as agarose (Kadonaga, *Methods Enzymol.*, 1991, *208*, 10; Arndt-Jovin *et al.*, *Eur. J. Biochem.*, 1975, *54*, 411; Wu *et al.*, *Science*, 1987, *238*, 1247; Blank *et al.*, *Nucleic Acids Res.*, 1988, *16*, 10283) or cellulose (Goldkorn *et al.*, *Nucl. Acids Res.*, 1986, *14*, 9171; Alberts *et al.*, *Meth. Enzymol.*, 1971, *21*, 198) or derivatives thereof, e.g., DEAE-cellulose (Schott, *J. Chromatogr.*, 1975, *115*, 461) or phosphocellulose (Siddell, *Eur. J. Biochem.*, 1978, *92*, 621; Bunemann *et al.*, *Nucl. Acids Res.*, 1982, *10*, 7163; Noyes *et al.*, *Cell*, 1975, *5*, 301; Bunemann *et al.*, *Nucl. Acids Res.*, 1982, *10*, 7181); dextran sulfate (Gingeras *et al.*, *Nucl. Acids Res.*, 1987, *15*, 5373); polypropylene (Matson *et al.*, *Anal. Biochem.*, 1994, *217*, 306); agarose beads (Kadonaga *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1986, *83*, 5889); latex particles (Kawaguchi *et al.*, *Nucleic Acids Res.*, 1989, *17*, 6229); nylon beads (Van Ness *et al.*, *Nucl. Acids Res.*, 1991, *19*, 3345); paramagnetic beads (Gabrielson *et al.*, *Nucl. Acids Res.*, 1989, *17*, 6253; Day *et al.*, *Biochem. J.*, 1991, *278*, 735); silica gels (Yashima *et al.*, *J. Chromatogr.*, 1992, *603*, 111); derivatized forms of silica gels, polytetrafluoroethylene, cellulose or metallic oxides (U.S. Patent No. 4,812,512 to Buendia); and art-recognized equivalents of any of the preceding solid supports. In one set of preferred embodiments, the solid support is a crosslinked copolymer of N-vinylpyrrolidone, other N-vinyl-lactam monomers and an ethylenically unsaturated monomer having at least one amine or amine-displacable functionality as disclosed in U.S. Patent No. 5,391,667. In another set of preferred embodiments, polystyrene or long chain alkyl CPG (controlled pore glass) beads are employed as the solid

dupport. In a further set of preferred embodiments, the support is soluble and is composed of, for example, modified polethylene glycol (PEG) units (Bonora *et al.*, *Nucleic Acids Res.*, 1993, *21*, 1213; Bagno *et al.*, *Chem. Biochem. Eng. Q.*, 1994, *8*, 183); PEG-based matrices having the advantage of being reversibly precipitable from solution.

With regard to the optional linker (2), a variety of chemical linking groups or chains may be employed in the matrix of the invention. Any chemical group or chain capable of forming a stable chemical linkage, or a stable association, between the support (1) and the affinity unit (4), or between the support (1) and the optional spacer (3), may be employed. A suitable linker has preferred characteristic of non-reactivity with compounds introduced during the various steps of oligonucleotide synthesis. It will be appreciated by those skilled in the art that the chemical composition of the support (1) and the affinity unit (4) and/or the optional spacer (3) may influence the choice of the linker. Many suitable linkers will comprise a primary amine group at either or both termini, as many chemical reactions are known in the art for linking primary amine groups to a variety of other chemical groups. However, other terminal reactive moieties are known and may be used in the invention. Suitable linkers include, but are not limited to, linkers having a terminal thiol group for introducing a disulfide linkages to the support (Day *et al.*, *Biochem. J.*, 1991, *278*, 735; Zuckermann *et al.*, *Nucl. Acids Res.*, *15*, 5305); linkers having a terminal bromoacetyl group for introducing a thiol-bromoacetyl linkage to the support (Fahy *et al.*, *Nucl. Acids Res.*, 1993, *21*, 1819); linkers having a terminal amino group which can be reacted with an activated 5' phosphate of an oligonucleotide (Takeda *et al.*, *Tetrahedron Letts.*, 1983, *24*, 245; Smith *et al.*, *Nucl. Acids Res.*, 1985, *13*, 2399; Zarytova *et al.*, *Anal. Biochem.*, 1990, *188*, 214); poly(ethyleneimine) (Van Ness *et al.*, *Nucl. Acids Res.*, 1991, *19*, 3345); acyl chains (Akashi *et al.*, *Chem. Lett.*, 1988, 1093; Yashima *et al.*, *J. Chromatogr.*, 1992,

603, 111); polyvinyl alcohol (Schott, *J. Chromatogr.*, 1975, *115*, 461); alkyl chains (Goss *et al.*, *J. Chromatogr.*, 1990, *508*, 279); alkylamine chains (Pon *et al.*, *BioTechniques*, 1988, *6*, 768); biotin-avidin or biotin-streptavidin linkages (Kasher *et al.*, *Mol. Cell. Biol.*, 1986, *6*, 3117; Chodosh *et al.*, *Mol. Cell. Biol.*, 1986, *6*, 4723; Fishell *et al.*, *Methods Enzymol.*, 1990, *184*, 328); and art-recognized equivalents of any of the preceding linkers. In a preferred embodiment of the invention, an *n*-aminoalkyl chain is the linker. In a particularly preferred embodiment of the invention, in which an oligonucleotide chain constitutes both the spacer (3) and the affinity unit, an *n*-aminohexyl chain [i.e., NH_2-$(CH_2)_6$] is the linker (2).

With regard to the optional spacer (3), a variety of chemical groups or chains may be employed in the matrix of the invention. Any chemical group or chain capable of forming a stable chemical linkage, or a stable association, between the support (1) and the affinity unit (4), or between the support (1) and the optional linker (2), may be employed. A suitable spacer has preferred characteristic of non-reactivity with compounds introduced during the various steps of oligonucleotide synthesis. It will be appreciated by those skilled in the art that the chemical composition of the support (1) and the affinity unit (4) and/or the optional linker (2) may influence the choice of the spacer. Typically suitable spacers include, but are not limited to, oligopeptides; oligonucleotides; alkyl chains; polyamines; polyethylene glycols; oligosaccharides; and art-recognized equivalents of any of the preceding spacers. In one set of preferred embodiments of the invention, the spacer is an alkyl chain, most preferably a C_1-C_{20} alkyl chain. In another set of preferred embodiments of the invention, the spacer is an oligonucleotide chain, particularly an oligonucleotide chain that comprises one or more chemical modifications that render it resistant to chemical attack. In this set of preferred embodiments, an oligodeoxyribonucleotide chain is particularly preferred. In a particularly preferred

embodiment of the invention, oligo$(dT)_{5-30}$ acts as the spacer of the matrix of the invention. This preferred spacer has the following advantages. This spacer is composed of nucleotides and is thus closely related in chemical properties to a preferred affinity unit, i.e., an oligonucleotide. This chemical relatedness provides the benefit of placing the affinity unit in a context that is likely to be appropriate for nucleic acid hybridization duplexing. Although other oligonucleotides [e.g., oligo(dA), oligo(dG) or oligo (dC)] might be employed for the spacer, a preferred spacer is more chemically stable.

It will be appreciated by those skilled in the art that the optional linker (2) and the optional spacer (3) can be combined into one unit. Furthermore, the linker and spacers need not comprise distinct chemical groups or chains. For example, an appropriate oligopeptide or oligonucleotide chain could function as a combined linker and spacer of the matrix of the invention. Thus, suitable linker/spacers include, but are not limited, to the linker and spacers described above. Methods of determining an appropriate (i.e., providing the optimal degree and specificity of hybridization between the affinity unit and the target oligonucleotide) length of linker/spacers are known in the art (see, for example, Day *et al.*, *Biochem. J.*, 1991, *278*, 735). In general, however, for oligonucleotide synthetic conditions that include basic conditions, the linker (2) or spacer (3) of the matrix of the invention would not include carbonate groups. The carbonate moiety is relatively unstable to basic reagents used in some oligonucleotide syntheses and to contaminants (mainly bases) that may be found in solvents utilized in such oligonucleotide synthesis.

With regard to the affinity unit (4), this portion of the matrix of the invention has the characteristic of binding specifically (or at least preferentially) yet reversibly to a portion of a target oligonucleotide, the purification of the target oligonucleotide being the object

of the invention. The portion of the target oligonucleotide that is specifically bound by the affinity unit is referred to as its "hybridizing portion" herein. A preferred affinity unit is one that comprises a chemical composition having a nucleobase sequence that is the reverse complement of the hybridizing portion of the nucleobase sequence of the target oligonucleotide. The hybridizing portion may be a central portion, a terminal portion, or the majority or even entirety of the nucleobase sequence of the target oligonucleotide. The term "a central portion" is intended to encompass preferably from at least five, or from at least ten, contiguous nucleobases derived from the section of the target oligonucleotide's sequence that is internal from the target oligonucleotide's 3' and 5' "terminal portions." A terminal portion includes the most 3' or 5' nucleobase of a target oligonucleotide and comprises an additional number, r, of immediately contiguous nucleobases of the target oligonucleotide, wherein r is from 2 to about 10 nucleobases. An affinity unit having a nucleobase sequence that is the reverse complement of a central portion of the nucleobase sequence of the target oligonucleotide will hybridize with high affinity to the target oligonucleotide, but not to, e.g., deletion derivatives lacking one or more nucleobases in the central portion. In another embodiment, the nucleobase sequence of the affinity unit is "full-length", i.e., the same length (n) of the target oligonucleotide, and which is the reverse complement of that of the target oligonucleotide. Alternatively, the nucleobase sequence of the affinity oligonucleotide can be "essentially full-length", i.e., having a length, p, wherein p is a positive whole number ranging from 4 to n+4, wherein, in a duplex between the target oligonucleotide and the nucleobase sequence of the affinity oligonucleotide, neither the 5' overhang nor the 3' overhang of said target oligonucleotide is greater than two nucleobases, provided that, over length p, the nucleobase sequence of the affinity oligonucleotide is the reverse complement of the nucleotide

sequence of the target oligonucleotide. The nucleobase sequence of the affinity unit can be from 5 to 60 nucleobases in length, preferably from 10 to 40 nucleobases in length, more preferably from 11 to 30 nucleobases in length and most preferably from 12 to 25 nucleobases in length. Affinity units of differing chemical compositions (e.g., oligodeoxynucleotides, oligoribonucleotides and peptide nucleic acids) can be employed in the invention, although certain compositions may be preferred in particular instances. For example, when nucleases are suspected of being present in the initial mixture from which the target oligonucleotide is to be purified, or when nucleases from biological contaminants might eventually be present in a matrix that is stored and reused, compositions that are relatively nuclease resistant might be preferred. Such relatively nuclease resistant compositions include, for example, oligodeoxyribonucleotides and peptide nucleic acids. Unlike RNA nucleases, for which no "universal" inhibitor is known, all characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents such as EDTA (Jarrett, *J. Chromatogr.*, 1993, *618*, 315); oligodeoxyribonucleotides can thus be more simply prevented from nuclease degradation than oligoribonucleotides. Peptide nucleic acids, which are not degraded by either nucleases or proteases, exhibit particularly stringent specificities for their complementary oligonucleotides, and may thus provide the best separation from undesired derivative oligonucleotides in some instances.

The method of synthesis of the affinity unit does not typically effect the methods of the invention; in general, any method of synthesis of the particular sort of affinity unit, including methods for the solution phase synthesis of oligonucleotides (see U.S. Patent No. 5,210,264 to Yau, assigned to the present applicants; Reese *et al.*, *J. Chem. Soc. Perkin Trans.*, 1993, *1*, 2291; and Wada *et al.*, *Tetrahedron*, 1993, *49*, 2043) may be used. After its

synthesis, the affinity unit (or, if both the spacer portion and affinity unit are oligonucleotidic) is purified by HPLC (high pressure liquid chromatography). Because the presence of deletion derivatives in the affinity unit may result in the undesired binding and retention of deletion derivatives of the target oligonucleotide, it may be necessary to purify the affinity unit in a manner that achieves significant purity thereof at the expense of a reduced yield of the affinity unit. On the other hand, certain embodiments of the invention are more tolerant of impurities in the affinity unit than others. For example, purification of oligonucleotides via multiple rounds of affinity chromatography, wherein a different affinity unit is used during each round of purification (see Example 8), exposes the target oligonucleotide to two or more "screens" (matrices) with one likely result being a further removal of contaminating impurities from the target oligonucleotide mixture.

By stating that the oligonucleotide of the affinity unit has a sequence that is the "reverse complement" of that of the nucleotide sequence, the following features are intended. As is known in the art, a nucleic acid duplex is formed of two antiparallel strands, i.e., strands that hybridize to each other in a "head-to-tail" fashion:

```
Strand 1:   5' ----------------------------> 3'
Strand 2:   3' <---------------------------- 5'
```

Specific nucleobases in the interior of a nucleic acid duplex bind to specific partner nucleobases. Among the naturally occurring nucleobases, guanine (G) binds to cytosine (C), and adenine (A) binds to thymine (T) or uracil (U). Thus, in the above diagram, Strand 2 will have a nucleotide sequence that is the reverse complement of Strand 1, i.e., Strand 2 will have, in "reverse" (3' to 5') order, the partner ("complement") nucleobases to those of Strand 1.

The sequence of the oligonucleotide of the affinity unit can have reverse complementarity to the target oligonucleotide through a variety of equivalents. In addition to the equivalency of U (RNA) and T (DNA) as partners for A, other naturally occurring nucleobase equivalents are known, including 5-methylcytosine, 5-hydroxymethylcytosine (HMC), glycosyl HMC, gentiobiosyl HMC (C equivalents), and 5-hydroxymethyluracil (U equivalent). Furthermore, synthetic nucleobases which retain partner specificity are known in the art and include, for example, 7-deaza-guanine, which retains specificity for C. Thus, reverse complementarity will not be altered by any chemical modification to a nucleobase in the nucleotide sequence of the affinity oligonucleotide which does not alter its specificity for the partner nucleobase in the target oligonucleotide. Moreover, in instances when the target oligonucleotide comprises a mixture of nucleobases at one or more positions within its sequence, reverse complementarity can be achieved by inserting a "universal" base partner, e.g., hypoxanthine (inosine, I, is the corresponding nucleotide) at the corresponding position in the affinity unit. By way of example, an affinity unit having an affinity oligonucleotide having the nucleotide sequence 5'-GGGICGCG has a sequence that is the reverse complement of the target oligonucleotide mixture [5'-CGCGACCC, 5'-CGCGGCCC, 5'-CGCGTCCC and 5'-CGCGCCCC].

In embodiments wherein the nucleobase sequence of the affinity unit is essentially full-length, the duplex between the nucleobase sequence of the affinity unit and the hybridizing portion of the target oligonucleotide will result in the target oligonucleotide having either a "3' overhang" or a "5' overhang" or, in some instances, both types of overhangs. A "3' overhang" consists of unpaired nucleotides on the 3' terminus of the target oligonucleotide, whereas a "5' overhang" consists of unpaired nucleotides on the 5' terminus of the target oligonucleotide. The two types of overhangs may be

diagramed as follows:

3' overhang of target oligonucleotide:

```
                                                    3'
                                                |-overhang-|
Target (length n):          5' ------------------------------> 3'
Affinity unit (length p): 3' <---------------- 5'
```

5' overhang of target oligonucleotide:

```
                                  5'
                              |-overhang-|
Target (length n):          5' ------------------------------> 3'
Affinity unit (length p): 3'                <---------------- 5'
```

It will be appreciated by those skilled in the art that a preferred affinity unit will selectively bind and/or retain the target oligonucleotide with high affinity and specificity under conditions wherein derivatives of said target oligonucleotide having one or more mismatches with the nucleobase sequence of said affinity unit are not bound and/or retained. In various embodiments of the invention, the affinity unit can incorporate one or more chemical modifications for the purpose of enhancing specific interactions with the target oligonucleotide, as is described in more detail in Example 6. Such modifications may additionally or alternatively result in the affinity unit having increased resistance to degradative contaminants, e.g., exonucleases. The target oligonucleotide may additionally or alternatively comprise such modifications, so long as reverse complementarity is maintained between the target oligonucleotide and that of the affinity unit over the above-defined "hybridizing" portion of the target oligonucleotide or lengths "n" (full-length) or "p" (essentially full-length) thereof.

It will be appreciated by those skilled in the art that the optional linker (2), optional spacer (3) and affinity unit (4) can be combined into one unit.

Furthermore, the linker, spacer and affinity unit need not comprise distinct chemical groups or chains. For example, an appropriate oligonucleotide chain could function as the linker, spacer and affinity unit of the matrix of the invention.

It will be further appreciated by those skilled in the art that the probe of the matrix of the invention, comprising affinity unit (4) and, optionally, the spacer (3), can be combined into one unit. Furthermore, the spacer and affinity unit need not comprise distinct chemical groups or chains. Thus, in a preferred embodiment, an aminohexyl group is the linker (2) to the support (1), as it is easily attached to the 5' end of a oligonucleotide by a solid phase synthesizer. In this embodiment, which is described in more detail in the Examples, the probe includes an oligonucleotide which comprises a first nucleotide sequence, which functions as the spacer (3), and a second nucleotide sequence, which serves as the affinity unit (4).

It will also be appreciated by those skilled in the art that the affinity unit (4) can be attached to the spacer (3), linker (2) or support (1) at any position thereof so long as the potential for hybridization with the target oligonucleotide is not negatively effected. That is, the affinity unit can be attached to the spacer, linker or support at its 3' or 5' terminus, or through a position on its backbone or one or more of its sugar residues or nucleobases, so long as the portion of the affinity unit that hybridizes to the hybridizing portion of the target oligonucleotide remains accessible for binding.

In one embodiment, the affinity unit (4) is synthesized directly on the support (i.e., *in situ*) rather than being separately synthesized and subsequently attached to the support. This embodiment is particularly useful when the components of the affinity unit, and the components linking it to the support, are stable under the various conditions of synthesis and subsequent chemical steps (deprotection, deblocking and the like) necessary to prepare

the matrix for use in the method of the invention. Examples of *in situ* synthesis of oligonucleotides on both soluble and insoluble supports are known in the art (Bonora *et al.*, *Nucleic Acids Res.*, 1993, *21*, 1213; Bagno *et al.*, *Chem. Biochem. Eng. Q.*, 1994, *8*, 183; Matson *et al.*, *Anal. Biochem.*, 1994, *217*, 306; Maskos *et al.*, *Nucl. Acids Res.*, 1992, *20*, 1679; Southern *et al.*, *Genomics*, 1992, *13*, 1008; Sheldon *et al.*, *in: Matrix DNA Hybridization, Nucleic Acid Conference*, San Diego, 1992; Cashion *et al.*, *Nucl. Acids Res.*, 1977, *4*, 2593; Duncan *et al.*, *Anal. Biochem.*, 1988, *169*, 104).

The method of the invention comprises at least 2 steps: (a) contacting a mixture comprising the target oligonucleotide and undesired deletion sequence oligonucleotides to the matrix of the invention under conditions such that a hybridization reaction preferentially occurs between the target oligonucleotide and the affinity unit, and (c) dissociating and recovering the target oligonucleotide from the matrix of the invention. Optionally, the method of the invention additionally comprises step (b), removing unbound, undesired deletion sequence oligonucleotides or other undesirable contaminants from the matrix by, for example, washing the matrix while the target oligonucleotide is bound thereto.

Step (a) is a hybridization step in which a mixture of crude synthetic oligonucleotides, comprising the desired full length n-mer as well as undesired derivatives [i.e., (n-1), (n-2), etc.] is contacted to the matrix of the invention and allowed to hybridize to the affinity unit. The degree of hybridization between the affinity unit and the full length (n) target oligonucleotide is dependent upon parameters such as the ionic strength of the buffer solution in which the hybridization occurs, temperature, base composition and length of the duplex formed between the target oligonucleotide and the affinity unit, concentration of the affinity unit, concentration of the target oligonucleotide, and the concentration(s) of duplex

destabilizing agent(s). The method of the invention is designed to maximize the affinity of the affinity unit for the full length target oligonucleotide while achieving the least degree of affinity for undesired (deletion sequence) oligonucleotides.

The following serve as examples of the buffer solution can be applied:

(1) SSPE buffer (1x-5x); 5x SSPE buffer is 0.75 M NaCl, 50 mM NaH_2PO_4, pH 7.4, and 5 mM EDTA; and

(2) 1 M KOAc or NaOAc buffer, pH 6.5.

As will be appreciated to those skilled in the art, it is preferable to remove nucleases and duplex destabilizing agents from such buffers before their use in hybridization reactions. This can be achieved by, for example, autoclaving the buffers.

Temperature can be another important parameter for hybridization reactions. In the method of the invention. In certain preferred embodiments of the invention, the temperature of the hybridization reaction is adjusted so that only full length target oligonucleotide will quantitatively hybridize to the affinity unit. At optimum temperatures, the formation of duplexes between the affinity unit and undesired oligonucleotides (deletion sequences) will be thermodynamically disfavored. Although, as is known in the art, optimum temperatures can be estimated for various chromatographic methods involving nucleic acids, some degree of "fine tuning" will be required in many instances. For example, Jarrett (*J. Chromatogr.*, 1993, *618*, 315) opines that the equation given by Sambrook *et al.* (*Molecular Cloning-A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2nd Ed., 1989, pages 9.47-9.51) is "the most useful" in chromatography experiments, but notes that "[s]ome cautions must apply to the use of these equations."

The methods of the invention optionally comprise the step (b), removing undesired oligonucleotides and/or other undesired contaminants, which may be carried out, for example, by placing the hybridized matrix:target oligonucleotide complexes into a suitable washing buffer which has a composition that is similar, or even identical, to that of the hybridization buffer of step (a) but which is different in concentration. When identical in composition to the hybridization buffer, the washing buffer can be from 0.4x to 2x, preferably from 0.5x to 1.6x, and most preferably from 0.6x to 1.2x the concentration of the hybridization buffer. By way of example, if the hybridization buffer is 3x SSPE buffer, the washing buffer is from 1.2x to 6x SSPE buffer, preferably from 1.5x to 4.8x SSPE buffer, and most preferably from 1.8x to 3.6x SSPE buffer. In an alternative embodiment, the temperature at which the hybridization reaction occurs is increased so that undesired oligonucleotides do not hybridize as well to the affinity unit. In general, the temperature for hybridization reactions should be between the melting temperature of the full length oligonucleotide duplex, T_m^n, and the highest melting temperature of deletion sequence oligonucleotides, T_m^d. That is, the temperature range at which the hybridization reaction is performed, T, is defined by the equation

$$T_m^d < T < T_m^n.$$

Methods for estimating and determining these parameters are known in the art (see, for example, Lehninger, *Biochemistry*, 2nd Ed., *1970*, Worth Publishers Inc., New York, NY, page 875; Jarrett, *J. Chromatogr.*, 1993, *618*, 315; Freier, Chapter 5 *In: Antisense Research and Applications*, Crooke et al., Eds., *1993*, CRC Press, Boca Raton, LA, pp. 67-82). The purpose of optional step (b) is to remove as many deletion sequence oligonucleotide molecules and other undesirable contaminating molecules as possible while maintaining the

highest possible concentration of hybridized full length oligonucleotide bound to the affinity unit of the support. Accordingly, the specific conditions at which these steps are carried out may be adjusted by monitoring these parameters and others known to those skilled in the art.

Step (c), dissociation and recovery of the full length target oligonucleotide, is achieved, for example, by placing the matrix:target oligonucleotide complexes into distilled water. The target oligonucleotide is thus easily and readily dissociated from the matrix of the invention and is recovered in the distilled water. Temperature and time are two parameters that can be adjusted to achieve optimal elution. In a preferred embodiment, the full length oligonucleotide is dissociated and recovered (1) in distilled water, ensuring a low salt content in the final product and thus eliminating an expensive desalting step, and (2) at a temperature higher than that at which the hybridization step (a) occurred in order to facilitate the complete release of the target oligonucleotide. This preferred embodiment eliminates the need for an expensive and time-consuming desalting step that is present in many other methods of oligonucleotide purification. If desired, the presence of oligonucleotides in the flow-through during the recovery step (c), or any other step(s), can be monitored by a variety of methods known in the art (see, for example, Jarrett, *J. Chromatogr.*, 1993, *618*, 315).

In a preferred embodiment of the invention, the methods and matrices of the invention are used to purify oligonucleotides prepared by a synthesis procedure that is "blockwise," i.e., one in which one or more coupling steps results in the incorporation of a "blockmer" of nucleobase units (e.g., a dinucleotide or trinucleotide). As used herein, a "blockmer" refers to a chemically linked sequence of 2, 3, 4, 5, 6, 7 or 8 nucleobases that is incorporated into an oligonucleotide *en toto*. Oligonucleotide synthesis procedures that utilize at least one step in which several nucleobases are incorporated in one step are known in the

art (see, e.g., Kumar *et al.*, *J. Org. Chem.*, 1984, *49*, 4905; Bannwarth, *Helv. Chimica Acta*, 1985, *68*, 1907; Cosstick *et al.*; *Biochemistry*, 1985, *24*, 3630; Wolter *et al.*, *Nucleosides & Nucleotides*, 1986, *5*, 65; Miura *et al.*, *Chem. Pharm. Bull.*, 1987, *35*, 833; Yau *et al.*, *Tetrahedron Letts.*, 1990, *31*, 1953).

The purification, by the methods and materials disclosed herein, of target oligonucleotides prepared by blockwise synthesis procedures (in contrast to synthesis procedures which incorporate a single nucleobase per coupling step) is a preferred embodiment of the invention for the following reasons. A synthesis procedure that couples, for example, dinucleotides rather than mononucleotides results in a final reaction mixture wherein the contaminating undesired products are, for the most part, (n-2), (n-4), (n-6), *etc.* in length relative to the desired n-mer target oligonucleotide. Like all final reaction mixtures resulting from blockwise synthesis procedures, an [(n-2), (n-4), (n-6), *etc.*] mixture has the inherent advantage over final reaction mixtures comprising (n-1) derivatives, because some (n-1) derivatives can be particularly difficult to separate from the desired n-mer. The method of purification of a desired target oligonucleotide of the invention, which is effective in selectively removing single base (n-1) deletions from a mixture, is expected to be particularly effective when the method is applied to a "blockwise" final reaction mixture that has fewer undesired derivative oligonucleotides of the (n-1) type, albeit containing undesired derivative oligonucleotides having deletions greater than one nucleobase [i.e., (n-2), (n-3), (n-4), (n-5) or (n-6) bases]. Furthermore, it is possible in some instances to "fix" a desired chemical feature (e.g., a stereospecific chemical linkage) in a blockmer unit that would otherwise be randomized by the coupling steps required to get the two or more nucleobases of the blockmer incorporated into desired oligonucleotide. Finally, because they require fewer

condensation (coupling) steps, blockwise procedures should produce final reaction mixtures that contain fewer non-nucleobase containing contaminants (e.g., solvents) as well, a feature that further enhances the use of such procedures with the methods and materials of the invention herein disclosed.

EXAMPLES

The following examples illustrate the invention and are not intended to limit the same. Those skilled in the art will recognize, or be able to ascertain through routine experimentation, equivalents to the specific substances and procedures described. Such equivalents are considered to be within the scope of the present invention.

Example 1: Affinity Design

The matrix of the invention consists of several parts: a support (1), an optional linker (2) to the support, an optional spacer (3) and an affinity unit (4) designed to specifically hybridize to the target oligonucleotide. The probe of the matrix of the invention comprises parts (4) and, optionally, (3). In Examples 1 to 3, all four parts are used. An aminohexyl group, a preferred linker (2) to the support (1), as it is easily attached to the 5' end of a oligonucleotide by a solid phase synthesizer, is used in Examples 1 to 3. In one embodiment of the invention, oligo$(dT)_{5-30}$ acts as the optional spacer (3); in Examples 1 to 3, $(dT)_{15}$ is used. As described in more detail herein, an oligomer complementary to the target oligonucleotide in sequence is a preferred affinity unit.

As one example, a matrix to purify ISIS 2302,

5'-GCC-CAA-GCT-GGC-ATC-CGT-CA
SEQ ID NO:1,

is represented as

[SS]-NH_2-$(CH_2)_6$-T_n-5'-TGA-CGG-ATG-CCA-GCT-TGG-GC-3',

wherein the nucleotide sequence of the affinity unit is SEQ ID NO:2, "[SS]" indicates the solid support (1) and n = 5-30. The affinity unit of this matrix will hybridize with ISIS 2302 to form a duplex of 20 base pairs (hybridization between bases is indicated by the "|" symbol):

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
||||||||||||||||||||
3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:2

Any (n-1), (n-2), etc. derivative of the desired oligonucleotide will have either one or more mismatches to the affinity unit or a shorter hybridizing sequence thereto. The following representative deletion sequences serve as illustrations of this principle (deleted nucleotides relative to SEQ ID NO:1 are indicated by an asterisk, "*"):

5'-GCC-CAA-GCT-G*C-ATC-CGT-CA
SEQ ID NO:3,

5'-*CC-CAA-GCT-GGC-ATC-CGT-CA
SEQ ID NO:4,

5'-GCC-CAA-GCT-**C-ATC-CGT-CA
SEQ ID NO:5,

5'-GCC-CAA-*CT-G*C-ATC-CGT-CA
SEQ ID NO:6, and

5'-GCC-CAA-GCT-GG*-***-***-**
SEQ ID NO:7.

Potential compromised hybridization structures

with the affinity unit are represented as follows (matches, i.e., paired bases, are indicated by "|" and mismatched or unmatched bases are represented as "."):

For SEQ ID NO:3, probable hybridization structures include

SEQ ID NO:3
5'-GCCCAAGCTGCATCCGTCA
||||||||||....|.....
3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:2,

a structure having only 11 "matches" (base pairs), or

SEQ ID NO:3
5'-GCCCAAGCTG CATCCGTCA
|||||||||| |||||||||
3'-CGGGTTCGAC GTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
\ /
C
SEQ ID NO:2,

a structure having 19 matches at the thermodynamic expense of forming a "bulge," i.e., excluding a single cytosine base from the structure. In any event, neither of these structures, nor any others that might be proposed, will comprise a 20 base pair hybridization structure as is found when the affinity unit binds oligonucleotide ISIS 2302 (SEQ ID NO:1).

For SEQ ID NO:4, probable hybridization structures include

SEQ ID NO:4
5'- CCCAAGCTGGCATCCGTCA
.||||||||||||||||||
3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:2,

a structure having only 19 matches.

For SEQ ID NO:5, probable hybridization structures include

SEQ ID NO:5

5'-GCCCAAGCTCATCCGTCA

||||||||||.....

3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]

SEQ ID NO:2,

a structure having only 9 matches, or

SEQ ID NO:5

5'-GCCCAAGCT CATCCGTCA

||||||||| |||||||||

3'-CGGGTTCGA GTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]

\ /

CC

SEQ ID NO:2,

a structure having 18 matches at the thermodynamic expense of forming a two base "bulge."

For SEQ ID NO:6, probable hybridization structures include

SEQ ID NO:6

5'- GCCCAACTGCATCCGTCA

...|.....||||||||||

3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]

SEQ ID NO:2,

a structure having only 11 matches, or

SEQ ID NO:6

5'- GCCCAACTG CATCCGTCA

..||.|.||| |||||||||

3'- CGGGTTCGAC GTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]

\ /

C

SEQ ID NO:2,

a structure having 15 matches at the thermodynamic expense of forming a one base "bulge," or

SEQ ID NO:6
5'-GCCCAA CTGCATCCGTCA
|||||| |||.....
3'-CGGGTT GACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
\ /
C
SEQ ID NO:2,

a structure having 10 matches and at the thermodynamic expense of forming a one base "bulge," or

SEQ ID NO:6
5'-GCCCAA CTG CATCCGTCA
|||||| ||| |||||||||
3'-CGGGTT GAC GTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
\ / \ /
C C
SEQ ID NO:2,

a structure having 18 matches at the thermodynamic expense of forming two one-base "bulges."

Finally, for SEQ ID NO:7, the probable hybridization structure is

SEQ ID NO:7
5'-GCCCAAGCTGG
|||||||||||.....
3'-CGGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:2,

a structure having only 11 matches.

As will be appreciated by those skilled in the art, the hybridization structures with one or more one- or

two-base "bulges" are unstable because of the steric hindrance(s) and thermodynamic consequence(s) of excluding a base from the duplex. Accordingly, although not wishing to be bound by any theory in particular, the hybridization structures that might preferentially form would be those having fewer matches but lacking "bulges."

Among undesired derivatives of the first oligonucleotide, purification of which is the object of the invention, the (n-1) deletion sequence with the terminal base deleted is the hardest to separate from the full length oligonucleotide. In that case, perfect matches will be formed for the terminal (n-1) deletion sequence compared with n perfect matches for the full length oligonucleotides. All of the other sequences will have either fewer matches and/or at least one mismatch, and, due to the formation of energetically disfavored duplexes with the affinity unit, thus can be separated from the full length oligonucleotide based on differential affinity.

Example 2: Preparation of Support:Activated Linker

Polystyrene, controlled pore glass (CPG) and polyethylene glycol (PEG), with PEG being reversibly precipitable, are some preferred supports. In this example, a solid support, a CPG bead with a terminal primary amine group (CPG, Inc., Lincoln Park, N.J.) was used as the support (1) and linker (2). The CPG bead has a mean pore diameter of 569 D and a volume of 1.44 ml/g. The surface area is 55 m^2/g, therefore, 10 mg of CPG beads has the same surface area as one 0.5 m x 0.5 m glass slide.

The primary amine of the linker was modified as follows. 1,4-phenylene diisothiocyanate was dissolved in 100 ml pyrimine and 900 ml dimethyl formamide and reacted with 49.81 mg CPG at 37°C for 3 hours. The concentration of 1,4-phenylene diisothiocyanate was in large excess to minimize the dimer formation. The modified CPG was washed once with acetone, twice with methanol, spun down to remove

the solvent, and allowed to dry. The linker of the resultant modified beads comprises a terminal isothiocyanate group.

Example 3: Immobilization of Probe

The probe, comprising the affinity unit (4) and optional spacer (3) is, in this example, an oligonucleotide that comprises a first oligonucleotide sequence, dT_n, where n is 15, that serves as the spacer, and a second oligonucleotide sequence, SEQ ID NO:2, that is the reverse complement of the target oligonucleotide (ISIS 2302) and which serves as the affinity unit. The probe further comprises a primary aminohexyl group, $-NH_2(CH_2)_6-$, which is attached to the spacer at the 5' position of the terminal thymine residue.

To the tube containing the solid support:activated linker (Example 2) was added 0.5 ml of probe (145.9 nmol/ml) solution in 1x Tris buffer (pH 8.0). The mixture was incubated at 37°C for 4 hours. Under these mildly alkaline conditions, the primary amine group of the probe reacted with the isothiocyanate group of the modified beads to form a thiocarbamyl adduct. The probe was thereby covalently attached to the surface of the solid support via the linker (Figure 2). Before and after immobilization, the concentration of the probe solution was measured by UV absorbtion at 260 nm. The calculation indicated that 52.42 nmol of probe had been immobilized or adsorbed onto the CPG. The immobilized CPG was washed by distilled water and 3.6 nmol of the probe was eluted. Therefore, the amount of the probe immobilized onto the CPG was 48.82 nmol.

Example 4: Hybridization, Extraction and Elution

In this Example, hybridization (step (a)) was achieved by adding 1 ml of 10 fold diluted crude ISIS 2302 in 3x SSPE buffer solution to the immobilized CPG, followed by incubation at 37°C for 4 hours. By measuring the absorbance of the solution before and after the

hybridization and after washing, it was determined that 46.9 nmol of ISIS 2302 had been hybridized to the probe on the support. A preferred hybridization structure is represented as follows:

SEQ ID NO:1

5'-GCCCAAGCTGGCATCCGTCA-3'

||||||||||||||||||||

3'-CGGGTTCGACCGTAGGCAGT-T_{15}-$(CH_2)_6$-NH_2-[CPG]

SEQ ID NO:2

The ratio of target oligonucleotide to the probe was 0.9607, that is to say, the efficiency of hybridization is 96%, or close to 1:1.

In some instances, it may be desirable to rinse the bound oligonucleotides before the recovery step (c) in order to enhance the removal of undesired derivative oligonucleotides or any other impurities. For example, the hybridized CPG may be washed once or twice with the extraction buffer. In this example, the removal (step (b)) of undesired oligonucleotides was accomplished as follows. The bound oligonucleotides were rinsed with 0.5 ml of 2x SSPE buffer. The rinse was performed 2x at 37°C.

After hybridization (step (a)) and removal of undesired and unbound contaminants (step (b)), hybridized ISIS 2302 was dissociated and recovered (step (c)) by incubation with distilled water at 90°C for 30 minutes. As is known by those skilled in the art, there are several means of dissociating bound synthetic oligonucleotide from the affinity unit of the invention. For example, a pH gradient could be used, starting at about pH 5 and finishing at about pH 10. Under these conditions, most target oligonucleotides and affinity units will be stable, and the pH of the resultant purified oligonucleotide can be easily adjusted before further use by, for example, dialysis. It will be further appreciated by those skilled in the art that the means of dissociating and recovering bound target

oligonucleotide will vary according to the chemical nature of the matrix and affinity unit being used. For example, the affinity unit may be or comprise a peptide nucleic acid (PNA). Because of the neutral charge of PNA, ammonium hydroxide can be added, at a concentration of from about 0.5% to about 10% (wt/vol), to a matrix to which target oligonucleotide is bound in order to effect dissociation of the target oligonucleotide from the matrix. Ammonium hydroxide can then be removed from the purified target oligonucleotide according to methods known in the art.

Example 5: Purity Analysis

The purity of the purified full length oligonucleotide was measured by capillary gel electrophoresis (CGE). Both crude and extracted ISIS 2302 solutions were analyzed by CGE. The resultant electropherograms (Figure 3, crude ISIS 2302; Figure 4, extracted ISIS 2303) show that the purity of the extracted oligonucleotide solution is much higher than the original one. The earlier eluting (n-1), (n-2), etc. undesired derivative oligonucleotides are to the left of the large, narrow peak of desired target oligonucleotide. Integration of the areas under the peaks indicates that the crude ISIS 2302 preparation contains 13.5% undesired derivative oligonucleotides. In contrast, ISIS 2302 purified by the method of the invention contains only 2.8% undesired derivative oligonucleotides. Thus, the purity of the desired target oligonucleotide has been increased from 86.5% to 97.2%.

To compare the results and evaluate the method of the invention, crude ISIS 2303, HPLC-purified ISIS 2303 and ISIS 2303 purified according to the method of the invention are electrophoretically separated under the same conditions.

Example 6: Modified Affinity Units

In this embodiment of the invention, one or more nucleotides of the affinity unit comprises at least one

chemical modification which (i) lowers the affinity of the probe for one or more undesired oligonucleotides but does not adversely impact the probe's affinity for the desired oligonucleotide, (ii) raises the affinity of the probe for the target oligonucleotide but does not enhance the probe's affinity for the undesired oligonucleotides, or (iii) achieves both of goals (i) and (ii).

Specific examples of some modified oligonucleotides that can be incorporated into the probe include those containing phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Specifically, oligonucleotides with phosphorothioates and those with CH_2-NH-O-CH_2, CH_2-N(CH_3)-O-CH_2 [known as a methylene(methylimino) or MMI backbone], CH_2-O-N(CH_3)-CH_2, CH_2-N(CH_3)-N(CH_3)-CH_2 and O-N(CH_3)-CH_2-CH_2 backbones, wherein the native phosphodiester backbone is represented as O-P-O-CH_2), oligonucleotides having morpholino backbone structures (Summerton and Weller, U.S. Patent 5,034,506) or a peptide nucleic acid (PNA) backbone (in which the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the nucleobases being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone (Nielsen *et al.*, *Science*, 1991, *254*, 1497), modified oligonucleotides containing one or more substituted sugar moieties [i.e., sugar moieties comprising one of the following at the 2' position: OH, SH, SCH_3, F, OCN, OCH_2OCH_3, $OCH_2O(CH_2)_nCH_3$, $O(CH_2)_nNH_2$ or $O(CH_2)_nCH_3$ where n is from 1 to about 10; C_1 to C_{10} lower alkyl, alkoxyalkoxy, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF_3; OCF_3; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; $SOCH_3$; SO_2CH_3; ONO_2; NO_2; N_3; NH_2; heterocycloalkyl; heterocycloalkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an

oligonucleotide and other substituents having similar properties], including 2'-*O*-methoxyethoxy [2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl)] (Martin et al., *Helv. Chim. Acta*, 1995, *78*, 486), 2'-methoxy (2'-O-CH_3), 2'-propoxy (2'-$OCH_2CH_2CH_3$) and 2'-fluoro (2'-F), or similar modifications made at other positions on the oligonucleotide (particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide), oligonucleotides having sugar mimetics such as cyclobutyls in place of the pentofuranosyl group or base modifications or substitutions (e.g., with a "universal" base such as inosine) can be used in this embodiment.

The target oligonucleotide may also comprise one or more the above modifications. A further modification of the target oligonucleotide involves chemically linking to the target oligonucleotide one or more lipophilic moieties which enhance the cellular uptake of the oligonucleotide. Such lipophilic moieties include but are not limited to a cholesteryl moiety (Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 1989, *86*, 6553), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Let.*, 1994, *4*, 1053), a thioether, e.g., hexyl-*S*-tritylthiol (Manoharan *et al.*, *Ann. N.Y. Acad. Sci.*, 1992, *660*, 306; Manoharan *et al.*, *Bioorg. Med. Chem. Let.*, 1993, *3*, 2765), a thiocholesterol (Oberhauser *et al.*, *Nucl. Acids Res.*, 1992, *20*, 533), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras *et al.*, *EMBO J.*, 1991, *10*, 111; Kabanov *et al.*, *FEBS Lett.*, 1990, *259*, 327; Svinarchuk *et al.*, *Biochimie*, 1993, *75*, 49), a phospholipid, e.g., di-hexadecyl-*rac*-glycerol or triethylammonium 1,2-di-O-hexadecyl-*rac*-glycero-3-H-phosphonate (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, *36*, 3651; Shea *et al.*, *Nucl. Acids Res.*, 1990, *18*, 3777), a polyamine or a polyethylene glycol chain (Manoharan *et al.*, *Nucleosides & Nucleotides*, 1995, *14*, 969), or adamantane acetic acid (Manoharan *et al.*, *Tetrahedron Lett.*, 1995, *36*, 3651), a palmityl moiety (Mishra *et al.*, *Biochim. Biophys. Acta*, 1995, *1264*, 229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol

moiety (Crooke *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, *277*, 923). Oligonucleotides comprising lipophilic moieties, and methods for preparing such oligonucleotides, are disclosed in U.S. Patents No. 5,138,045, No. 5,218,105 and No. 5,459,255.

The target oligonucleotide, an oligonucleotide present in the probe, or both, can also be oligonucleotides which are chimeric oligonucleotides including "gapmers" and "hemimers." Chimeric oligonucleotides are oligonucleotides which contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one terminal region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the intracellular target nucleic acid. In a "hemimer," a single terminal (either 5' or 3') region is so modified in the oligonucleotide structure. When both termini of the oligonucleotide are modified, the oligonucleotide is called a "gapmer" and the modified 5'- and 3'-terminal regions are referred to as "wings"; an additional, typically central, region (typically referred to as the "gap" or "core") of the oligonucleotide may serve as a substrate for cellular enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. In a gapmer, the 5' and 3' wings can be modified in the same or different manner depending on what properties it is desired to achieve.

A preferred modification in many chimeric oligonucleotides designed for antisense purposes is the inclusion of one or more residues modified at the 2' position. An example is the 2'-O-methyl modification, which, when incorporated into synthetic oligonucleotides, results in increased duplex stability (nearly 0.8 kcal/mol per modification) between such oigonucleotides and RNA targets. At the same time that it enhances the duplex stability between the oligonucleotide and an RNA target, however, the 2'-O-methyl modification slightly destabilizes

the duplex formed between the oligonucleotide and a DNA target (Freier, Chapter 5 *In: Antisense Research and Applications*, Crooke *et al.*, Eds., *1993*, CRC Press, Boca Raton, LA, pages 67-82).

Modifications that enhance the affinity for, and/or duplex stability with, RNA molecules are preferred for applications wherein such oligonucleotides are intended for antisense purposes, wherein the oligonucleotide is designed to selectively bind to, and modulate the expression of, a particular RNA species. In the methods of the invention, affinity units comprising nucleobase sequences complementary to such modified portions of target oligonucleotides are designed to reflect the chemical modification(s) present in the target oligonucleotide. In the case of 2'-O-methyl-modified oligonucleotides, for example, an affinity unit comprising RNA or RNA-like nucleotide units would, due to the differences in duplex stability between RNA and DNA targets, be preferable to one composed strictly of deoxyribonucleotides.

By "RNA-like" it is meant that such an oligonucleotide, or such portion thereof, has an ability to form a stable duplex with an RNA target that exceeds its ability to form a stable duplex with a DNA target under comparable conditions. The acronym "RLO" refers to "RNA-like oligonucleotide" herein. While not wishing to be bound by any particular theory, it is presently believed that RNA:RNA, RNA:RLO and RLO:RLO duplexes differ from DNA:DNA and DNA:RNA duplexes in several significant conformational respects (Lesnik *et al.*, *Biochemistry*, 1993, *32*, 7832; Lesnik *et al.*, *Biochemistry*, 1995, *34*, 10807), and that these conformational differences contribute to the relative stabilities of structurally distinct duplex partners. In any event, target antisense oligonucleotides (ASO's) comprising an RNA or RNA-like hybridizing portion are preferentially purified using a matrix having an affinity unit comprising a hybridizing portion with one or more the following modifications, which enhance the stability of

duplexes formed with such modified affinity units and RNA or RLO molecules, and/or enhance the affinity of such modified affinity units for RNA or RLO molecules, and are thus preferred. Conversely, target ASO's comprising one or more of the following modifications in their hybridizing portion are preferably purified using affinity units having an RNA or RNA-like structure in their corresponding hybridizing portions. For this embodiment, such preferred modifications include but are not limited to sugar modifications, backbone modifications, nucleobase modifications or combinations thereof.

A preferred group of sugar modifications are modified at the 2'position. These include 2'-fluoro substitutions; 2'-O-alkyl substitutions, particularly those with relatively small (i.e., C_1-C_{10}) substituent groups, e.g., 2'-O-allyl (2'-O-CH_2-CH=CH_2), 2'-O-butyl [2'-O-$(CH_2)_3CH_3$] and 2'-O-methyl (2'-O-CH_3) substitutions; 2'-O-methoxy-ethyl, (2'-O-CH_2CH_2-O-CH_3) substitutions; 2'-O-alkoxy-alkoxy [2'-O-$(CH_2CH_2O)_n(CH_2)_mCH_3$ substitutions, where m is from 0 to 6 and n is from 2 to 6; 2'-O-aminoalkyl [2'-O-(CH_2)-NH_2]; 2'-O-CH_2-CHR-X where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3; and an intercalating substituent, such as that present on 2'-O-anthraquinolylmethyl uridine. Other sugar modifications include, for example, 4'-6' methano carbocyclic derivatives.

Backbone modifications (modified linkages) include the polyamide backbone, PNA (peptide nucleic acid); -CH_2-CO-NCH_3-CH_2-; the methylene(methylimino) or MMI backbone (-CH_2-NCH_3-O-CH_2-); the dimethylhydrazino or MDH backbone (-CH_2-NCH_3-NCH_3-CH_2-); amide 3 (-CH_2-CO-NH-CH_2-) or amide 4 (-CH_2-NH-CO-CH_2-)-based backbones; phosphoryl linked morpholino backbone; phosphonate (-CH_2-PO_2X-O-, where X=O or S) linkages such as, e.g., those disclosed in U.S. Patent No. 5,610,289; formacetal/ketal type linkages, such as, for example, those disclosed in U.S. Patent No. 5,264,562; and backbones incorporating HNA (1,5-anhydrohexitol) (Herdewijn, *Liebigs Ann.*, 1996, 1337; published PCT patent application WO

96/05213).

Nucleobase modifications include 5-methyl-cytosine and uridine and thymine derivatives, including those having substitutions of the 5-methyl group, e.g., by a propynyl (-C≡C-CH_3) methylthiazole or amino-ethyl-3-acrylimido substituent and 2-thio uridine or thymidine. A combination of 2'-fluoro-5-propynyl deoxyuridine is especially preferred. Preferred purine modifications include 7-modified-7-deaza purines and 2-amino-adenosine.

Certain combinations of the above modifications are also preferred in this embodiment of the invention. These include, but are not limited to, amide 3 or MMI modified linkages having a 2'-O-methyl group on the "lower" sugar (i.e., the sugar 3' of the modified linkage) and amide 3 and MMI modified linkages having 2'-O-methyl groups on both the "upper" sugar (i.e., the sugar 5' of the modified linkage) and the lower sugar; MMI modified linakges having 2'-fluoro substitutions on the lower, upper or both sugars; oligonucleotides having alternating MMI and phosphodiester linkages, which have the properties of high nuclease resistance as well as enhanced affinity for and duplex stability with RNA and RNA-like targets; MMI modified linakges having 2' substitutions on both the upper and lower sugar that are different substitutions (for example, 2'-O-methyl on the upper sugar and 2'-fluoro on the lower sugar); MMI modified linkages having one or more 2'-methoxy ethyl substitutions; and 2'-fluoro, N3'->P5' phosphoramidite oligonucleotides (Schultz *et al.*, *Nucleic Acids Res.*, 1996, *24*, 2966).

For this embodiment of the invention, particularly preferred nucleobases include, but are not limited to, 2'-fluoro-propynyl uridine, substituted for uridine or thymine, and 2'-O-methyl, 2-amino-adenosine in substitution for adenosine. Among oligonucleotide-based affinity units, particularly preferred are 2'-O-methyl MMI backbones, 2'-O-methyl amide 3 backbones, and 2'-fluoro, N3'->P5' phosphoramidite oligonucleotides. While not wishing to be

bound by any particular theory, it has been suggested that oligonucleotides comprising certain of these modifications (e.g., amide 3 and amide 4) have the tendency to organize themselves, prior to hybridization, into conformations more favorable for duplex formation. In other instances, and again not wishing to be bound by any particular theory, it has been proposed that certain of these modifications favor the C3' *endo* pucker conformation which, it is believed, RNA:RNA and RNA:RLO duplexes adopt (Lesnik *et al.*, *Biochemistry*, 1993, *32*, 7832; Kawasaki *et al.*, *J. Med. Chem.*, 1993, *36*, 831; Griffey *et al.*, *In: carbohydrate Modificatons in Antisense Research*, Sagvhi *et al.*, eds., ACS Symp. Ser. 580, Amer. Chem. Socy., Washington, D.C., 1994, pp. 212-224). Yet another contribution, particularly in the case of nucleobase modifications, may come from other stabilizing effects, such as improved base stacking (Froehler *et al.*, *Tetrahedron Letts.*, 1992, *37*, 5307), although applicants do not wish to be bound by any particular theory or theories regarding such effects. It will also be appreciated by those skilled in the art that increased affinity between the hybridizing portions of the target oligonucleotide is desirable only up to the point where discrimination between properly matched and mismatched species begins to deteriorate. Those of ordinary skill in the art will be able to prepare particular applications of the invention wherein the affinity and duplex stability of the matrix of the invention specific are maximized while an acceptable degree of discrimination is retained.

The choice of modification(s) to be incorporated into the affinity unit is thus influenced by the chemical nature of the target oligonucleotide. Furthermore, modifications can be strategically placed within the affinity unit in order to maximize the separation of undesired oligonucleotides that are particularly refractory to separation from the desired full length oligonucleotide. For example, the hybridization structure of Example 4 is modified in the following manner:

SEQ ID NO:1

5'-GCCCAAGCTGGCATCCGTCA-3'

3'-CGGGTTCGACCGTAGGCAGT-T_{15}-$(CH_2)_6$-NH_2-[CPG]

SEQ ID NO:2,

where the underlined nucleotides in the affinity unit (SEQ ID NO:2) are ribonucleotides rather than deoxyribonucleotides, and the target oligonucleotide (SEQ ID NO:1) comprises terminal 2'-*O*-methoxyethoxy modifications, as indicated by the asterisks. It is known in the art that, in DNA duplexes, the presence of 2'-*O*-methoxyethoxy modifications has a slight negative effect on duplex stability; in contrast, in DNA:RNA duplexes, the 2'-*O*-methoxyethoxy modification increases duplex stability by about 0.8 kcal/mol per modification (Freier, chapter 5 in: *Antisense Research and Applications*, Crooke *et al.*, eds., CRC Press, Boca Raton, 1993, page 69). Thus, as a consequence of the choice of modifications to the target oligonucleotide and the affinity unit, the above hybridization structure has a significantly greater stability when bound to the desired target chimeric oligonucleotide than when bound to undesired (n-1) derivatives lacking a single terminal nucleotide, i.e.,

SEQ ID NO:1

5'- CCCAAGCTGGCATCCGTCA-3'

3'- CGGGTTCGACCGTAGGCAGT-T_{15}-$(CH_2)_6$-NH_2-[CPG]

SEQ ID NO:2

and

SEQ ID NO:1

5'-GCCCAAGCTGGCATCCGTC -3'

3'-CGGGTTCGACCGTAGGCAGT-T_{15}-$(CH_2)_6$-NH_2-[CPG]

SEQ ID NO:2.

Although these differences in affinity are also present when the affinity unit is not so modified, the degree of differential affinity is enhanced due to the modifications. In the above exemplars, the desired hybridization structure is expected to have an increased stability of about 0.8 kcal/mol when compared with either of the duplexes which incorporate an undesired terminal (n-1) oligonucleotide.

Example 7: Essentially Full-Length Affinity Oligonucleotides

Although the nucleobase sequence of the affinity unit may be "full-length", i.e., of the same length, n, as the target oligonucleotide, affinity units having "essentially full-length" nucleobase sequences may also be used. In this embodiment of the invention, the affinity unit has a nucleobase sequence that is of a length, p, that is less than the length, n, of the target oligonucleotide. However, the nucleobase sequence of the affinity unit is nonetheless the reverse complement of the target oligonucleotide over length p. Moreover, p is a number ranging from n-4 to n, wherein, in a duplex between the target oligonucleotide and the nucleobase sequence of the affinity unit, neither the 5' overhang nor the 3' overhang of said target oligonucleotide is greater than two nucleotides.

As exemplars, affinity units having essentially full-length nucleotide sequences for ISIS 2302 are given as SEQ ID NOS:8 to 15. These affinity oligonucleotides will form the following duplexes with the target oligonucleotide, ISIS 2302 (n = 20 nucleotides). For SEQ ID NOS: 8 and 9 (p = 19 nucleotides),

SEQ ID NO:1

5'- GCCCAAGCTGGCATCCGTCA

.|||||||||||||||||||

3'- GGGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]

SEQ ID NO:8;

and

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
||||||||||||||||||.
3'-CGGGTTCGACCGTAGGCAG -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:9.

For SEQ ID NOS: 10 to 12 (p = 18 nucleotides),

SEQ ID NO:1
5'- GCCCAAGCTGGCATCCGTCA
.||||||||||||||||||.
3'- GGGTTCGACCGTAGGCAG -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:10;

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
||||||||||||||||||..
3'-CGGGTTCGACCGTAGGCA -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:11;

and

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
..||||||||||||||||||
3'- GGTTCGACCGTAGGCAGT-T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:12.

For SEQ ID NOS: 13 and 14 (p = 17 nucleotides),

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
.||||||||||||||||||..
3'- GGGTTCGACCGTAGGCA -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:13;

and

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
..||||||||||||||||.
3'- GGTTCGACCGTAGGCAG -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:14.

Finally, for SEQ ID NO:15 (p = 16 nucleotides),

SEQ ID NO:1
5'-GCCCAAGCTGGCATCCGTCA
..||||||||||||||||..
3'- GGTTCGACCGTAGGCA -T_n-$(CH_2)_6$-NH_2-[SS]
SEQ ID NO:15.

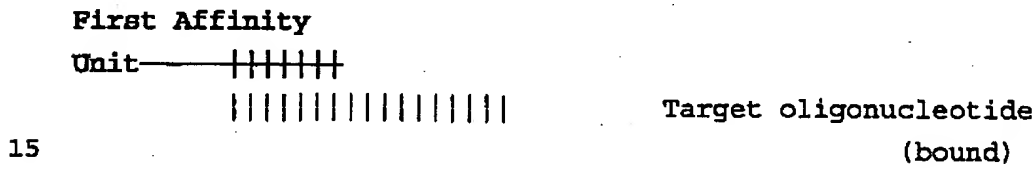
It will be appreciated by those skilled in the art that certain parameters (e.g., temperature of elution and extraction, etc.) will have to be adjusted to compensate for the loss of nucleobase partners in the affinity unit. Methods for estimating and determining these parameters are known in the art (see, for example, Lehninger, *Biochemistry*, 2nd Ed., *1970*, Worth Publishers Inc., New York, NY, page 875; Jarrett, *J. Chromatogr.*, 1993, *618*, 315; Freier, Chapter 5 *In: Antisense Research and Applications*, Crooke *et al.*, Eds., *1993*, CRC Press, Boca Raton, LA). Moreover, if desired, the presence of oligonucleotides in the flow-through during the extraction step (b) or elution step (c) can be monitored by a variety of methods known in the art. See, for example, Jarrett, *J. Chromatogr.*, 1993, *618*, 315.

Example 8: Repeated Rounds of Purification Using Different Affinity Units

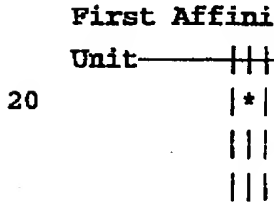
In some instances, it may be desirable to carry out multiple rounds of purification of a desired target

oligonucleotide by different matrices developed according to the present invention. As one example, for a longer target oligonucleotide, it may be difficult or expensive to develop one affinity unit, corresponding to an extended hybridizing portion of such a target oligonucleotide, of sufficient

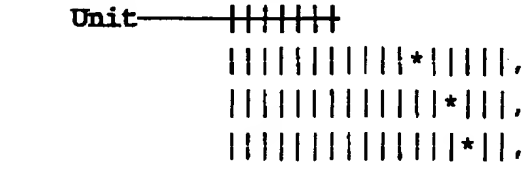
length and/or purity. Purification of a long oligonucleotide using an affinity unit that is less than full-length may result in the inclusion of mismatched derivatives that comprise mismatches (* in the diagram below) outside of the hybridizing portion of the target oligonucleotide:



Mismatched oligonucleotides not bound/retained are diagramed as follows:

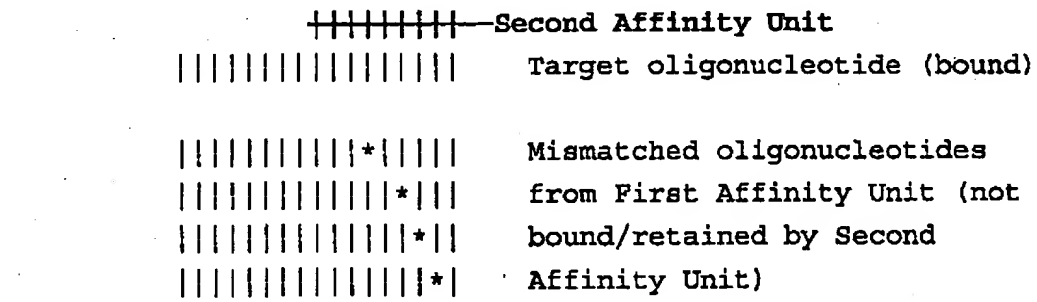


Mismatched oligonucleotides potentially bound/retained are diagramed as follows:



||||||||||||||*|, *etc.*

By applying the partially purified target oligonucleotide resulting from contacting and processing through a matrix comprising a first affinity unit to a matrix comprising a second affinity unit, wherein the first and second affinity units are complementary to different hybridizing portions of the target oligonucleotide, the mismatched oligonucleotides potentially bound and/or retained from the matrix comprising the first affinity unit are removed:



Although, in the above example, the affinity units are complementary to hybridizing portions of the target oligonucleotide located at 5' and 3' termini, no particular placement of the hybridizing portions is intended, other than that such hybridizing portions of the target oligonucleotide should typically be distinct from one another so that different undesirable contaminating derivatives of the target oligonucleotide are removed by each matrix. Thus, the first and second hybridizing portions can each be located at a 5' terminus, a 3' terminus, or within a central portion of the target oligonucleotide.

The temporal ordering of the two purification steps is not typically important; in the above scheme, for example, the "Second Affinity Unit" might just as well be used before the "First Affinity Unit" in most instances. Temporal ordering of the two purification steps may be a

consideration, however, when the matrices comprising the two affinity units are of different chemical composition and/or depending on the means used to dissociate and recover target oligonucleotide from the first affinity unit to which it is bound. For example, consider an instance wherein the eluent from affinity unit "A" is prepared in such a way so as to include one or more components (e.g., salts, solvents, ions, etc.) that would chemically disrupt the matrix into which affinity unit "B" is incorporated. In the latter instance, if the eluent from affinity unit "B" does not have such an effect on the matrix comprising affinity unit "A," it would be preferable to apply the mixture comprising the target oligonucleotide to matrix/affinity unit "B" before applying it to matrix/affinity unit "A."

It should also be appreciated by those skilled in the art that the number of affinity units and stepwise purifications need not be limited to two and that, in some instances, several such stepwise purifications, and appropriate affinity units and matrices, may be needed. Moreover, the two affinity units can be of the same or different chemical composition, depending on the chemical nature of the target oligonucleotide. For example, for a "hemimer" having a 3' portion comprising 2'-O-methoxy ethyl modified residues and a 5' portion comprising standard deoxyribonucleotide residues, the affinity unit for the RNA-like 3' hybridizing portion would preferably incorporate one or more of the modifications detailed in Example 6, whereas no such preference would exist for an affinity unit designed to hybridize to the DNA-like 5' portion of such an oligonucleotide. In fact, as will be appreciated by those skilled in the art, some of the modifications presented in Example 6 (e.g., 2'-O-methyl) actually lower the ability of the affinity unit to bind DNA and would thus be disfavored for affinity units designed to interact with a DNA-like hybridizing portion of a target oligonucleotide.

It will be further appreciated by those skilled in the art that the examples and embodiments described herein are for illustrative purposes only. Various modifications in light the disclosure will be suggested to persons skilled in the art and are intended to be included within the purview of the application and the scope of the claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Isis Pharmaceuticals, Inc. et al.

(ii) TITLE OF INVENTION: Large-Scale Purification of Full Length Oligonucleotides by Solid-Liquid Affinity Extraction

(iii) NUMBER OF SEQUENCES: 243

(iv) CORRESPONDENCE ADDRESS:

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(C) CITY: Philadelphia

(D) STATE: PA

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(F) ZIP: 19103

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: DISKETTE, 3.5 INCH, 1.44 MB STORAGE

(B) COMPUTER: IBM PS/2

(C) OPERATING SYSTEM: PC-DOS

(D) SOFTWARE: WORDPERFECT 6.1

(vi) CURRENT APPLICATION DATA:

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(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: John W. Caldwell

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(C) REFERENCE/DOCKET NUMBER: ISIS-2741

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (215) 568-3100

(B) TELEFAX: (215) 568-3439

(2) INFORMATION FOR SEQ ID NO: 1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: ISIS 2302
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER:
(I) FILING DATE:
(J) PUBLICATION DATE:
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:
GCCCAAGCTG GCATCCGTCA 20

(2) INFORMATION FOR SEQ ID NO: 2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:
TGACGGATGC CAGCTTGGGC 20

(2) INFORMATION FOR SEQ ID NO: 3:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Deletion derivative of SEQ ID NO: 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:
GCCCAAGCTG CATCCGTCA 19

(2) INFORMATION FOR SEQ ID NO: 4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Deletion derivative of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:
CCCAAGCTGG CATCCGTCA 19

(2) INFORMATION FOR SEQ ID NO: 5:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Deletion derivative of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:
GCCCAAGCTC ATCCGTCA 18

(2) INFORMATION FOR SEQ ID NO: 6:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Deletion derivative of SEQ ID NO: 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

GCCCAACTGC ATCCGTCA 18

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Deletion derivative of SEQ ID NO: 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GCCCAAGCTG G 11

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

TGACGGATGC CAGCTTGGG 19

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:
GACGGATGCC AGCTTGGGC 19

(2) INFORMATION FOR SEQ ID NO: 10:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:
GACGGATGCC AGCTTGGG 18

(2) INFORMATION FOR SEQ ID NO: 11:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:
ACGGATGCCA GCTTGGGC 18

(2) INFORMATION FOR SEQ ID NO: 12:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:
TGACGGATGC CAGCTTGG 18

(2) INFORMATION FOR SEQ ID NO: 13:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:
ACGGATGCCA GCTTGGG 17

(2) INFORMATION FOR SEQ ID NO: 14:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:
GACGGATGCC AGCTTGG 17

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Essentially full-length reverse complement of SEQ ID NO: 1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

ACGGATGCCA GCTTGG 16

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to c-myb mRNA; a.k.a. "MYB-AS"

(x) PUBLICATION INFORMATION:

(A) AUTHORS: Calabretta, Bruno, et al.

(B) TITLE: Inhibition of Protooncogene Expression in Leukemic Cells: An Antisense Approach

(C) JOURNAL: Antisense Research and Applications, Crooke, S.T., et al., eds., CRC Press, Boca Raton

(D) VOLUME: Chapter 31

(F) PAGES: 535-545

(G) DATE: 1993

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GTGCCGGGGT CTTCGGGC 18

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 16
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:
GCCCGAAGAC CCCGGCAC 18

(2) INFORMATION FOR SEQ ID NO: 18:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to mammalian DNA methyl transferase
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/15378 (SEQ ID NO: 1)
(I) FILING DATE: 30-NOV-1994
(J) PUBLICATION DATE: 08-JUN-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:
CATCTGCCAT TCCCACTCTA 20

(2) INFORMATION FOR SEQ ID NO: 19:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse

complement of SEQ ID NO: 18

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

TAGAGTGGGA ATGGCAGATG 20

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to mammalian DNA methyl transferase

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/15378 (SEQ ID NO: 2)

(I) FILING DATE: 30-NOV-1994

(J) PUBLICATION DATE: 08-JUN-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

TTGGCATCTG CCATTCCCAC TCTA 24

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

TAGAGTGGGA ATGGCAGATG CCAA 24

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 1)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:
CATGGTTTCG GAGGGCGTC 19

(2) INFORMATION FOR SEQ ID NO: 23:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 22
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:
GACGCCCTCC GAAACCATG 19

(2) INFORMATION FOR SEQ ID NO: 24:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF); a.k.a. "Vm"

(x) PUBLICATION INFORMATION:
(A) AUTHORS: Robinson, G.S., et al.
(B) TITLE: Oligodeoxynucleotides inhibit retinal neovascularization in a murine model of proliferative retinopathy
(C) JOURNAL: The Proceedings of the National Academy of Sciences (U.S.A.)
(D) VOLUME: 93
(F) PAGES: 4851-4856
(G) DATE: MAY-1996
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 2)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:
CAGCCTGGCT CACCGCCTTG G 21

(2) INFORMATION FOR SEQ ID NO: 25:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 24
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:
CCAAGGCGGT GAGCCAGGCT G 21

(2) INFORMATION FOR SEQ ID NO: 26:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes

(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(A) AUTHORS: Robinson, G.S., et al.
(B) TITLE: Oligodeoxynucleotides inhibit retinal neovascularization in a murine model of proliferative retinopathy (SEQ ID NO: M3)
(C) JOURNAL: The Proceedings of the NationaL Academy of Sciences (U.S.A.)
(D) VOLUME: 93
(F) PAGES: 4851-4856
(G) DATE: MAY-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:
TCGCGCTCCC TCTCTCCGGC 20

(2) INFORMATION FOR SEQ ID NO: 27:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 26
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:
GCCGGAGAGA GGGAGCGCGA 20

(2) INFORMATION FOR SEQ ID NO: 28:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 4)

(I) FILING DATE: 26-JUL-1994

(J) PUBLICATION DATE: 09-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

CACCCAAGAG AGCAGAAAGT 20

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 28

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

ACTTTCTGCT CTCTTGGGTG 20

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)

(x) PUBLICATION INFORMATION:

(A) AUTHORS: Nomura, M., et al.

(B) TITLE: Possible Participation of Autocrine and Paracrine Vascular Endothelial Growth factors in Hypoxia-induced Proliferation of Endothelial Cells

and Pericytes
(C) JOURNAL: The Journal of Biological Chemistry
(D) VOLUME: 270
(E) ISSUE 47
(F) PAGES: 28316-28324
(G) DATE: 24-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:
CCCAAGACAG CAGAAAGTTC AT 22

(2) INFORMATION FOR SEQ ID NO: 31:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 30
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:
ATGAACTTTC TGCTGTCTTG GG 22

(2) INFORMATION FOR SEQ ID NO: 32:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 5)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

TCGTGGGTGC AGCCTGGGAC 20

(2) INFORMATION FOR SEQ ID NO: 33:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 32
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:
GTCCCAGGCT GCACCCACGA 20

(2) INFORMATION FOR SEQ ID NO: 34:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 11)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:
CTGCCCGGCT CACCGCCTCG G 21

(2) INFORMATION FOR SEQ ID NO: 35:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 34

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

CCGAGGCGGT GAGCCGGGCA G 21

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 12)

(I) FILING DATE: 26-JUL-1994

(J) PUBLICATION DATE: 09-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

CATGGTTTCG GAGGCCCGA 19

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 36

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

TCGGGCCTCC GAAACCATG 19

(2) INFORMATION FOR SEQ ID NO: 38:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 13)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:
CACCCAAGAC AGCAGAAAGT 20

(2) INFORMATION FOR SEQ ID NO: 39:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 38
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:
ACTTTCTGCT GTCTTGGGTG 20

(2) INFORMATION FOR SEQ ID NO: 40:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes

(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 17)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:
CCATGGGTGC AGCCTGGGAC 20

(2) INFORMATION FOR SEQ ID NO: 41:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 40
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:
GTCCCAGGCT GCACCCATGG 20

(2) INFORMATION FOR SEQ ID NO: 42:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Vascular Endothelial Growth factor (VEGF)
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/04142 (SEQ ID NO: 17)
(I) FILING DATE: 26-JUL-1994
(J) PUBLICATION DATE: 09-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:
CCATGGGTGC AGCCTGGGAC 20

(2) INFORMATION FOR SEQ ID NO: 43:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 42
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:
GTCCCAGGCT GCACCCATGG 20

(2) INFORMATION FOR SEQ ID NO: 44:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 1)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:
CCCTTCCTAC CGCGTGCGAC 20

(2) INFORMATION FOR SEQ ID NO: 45:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 44

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

GTCGCACGCG GTAGGAAGGG 20

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to bcl-2 mRNA

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 3)

(I) FILING DATE: 20-SEP-1994

(J) PUBLICATION DATE: 30-MAR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

CCTCCGACCC ATCCACGTAG 20

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 46

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

CTACGTGGAT GGGTCGGAGG 20

(2) INFORMATION FOR SEQ ID NO: 48:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 5)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:
GTTGACGTCC TACGGAAACA 20

(2) INFORMATION FOR SEQ ID NO: 49:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 48
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:
TGTTTCCGTA GGACGTCAAC 20

(2) INFORMATION FOR SEQ ID NO: 50:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to bcl-2 mRNA

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 8)

(I) FILING DATE: 20-SEP-1994

(J) PUBLICATION DATE: 30-MAR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

CGCGTGCGAC CCTCTTG 17

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 50

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

CAAGAGGGTC GCACGCG 17

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to bcl-2 mRNA

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 9)

(I) FILING DATE: 20-SEP-1994

(J) PUBLICATION DATE: 30-MAR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

TCCTACCGCG TGCGACC 17

(2) INFORMATION FOR SEQ ID NO: 53:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 52
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:
GAGGGTCGCA CGCGGTA 17

(2) INFORMATION FOR SEQ ID NO: 54:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 10)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:
TCCTACCGCG TGCGACC 17

(2) INFORMATION FOR SEQ ID NO: 55:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 54

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

GGTCGCACGC GGTAGGA 17

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to bcl-2 mRNA

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 11)

(I) FILING DATE: 20-SEP-1994

(J) PUBLICATION DATE: 30-MAR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

CCTTCCTACC GCGTGCG 17

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 56

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

CGCACGCGGT AGGAAGG 17

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 12)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:
GACCCTTCCT ACCGCGT 17

(2) INFORMATION FOR SEQ ID NO: 59:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 58
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:
ACGCGGTAGG AAGGGTC 17

(2) INFORMATION FOR SEQ ID NO: 60:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 13)

(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:
GGAGACCCTT CCTACCG 17

(2) INFORMATION FOR SEQ ID NO: 61:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 60
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: BC-RC:
CGGTAGGAAG GGTCTCC 17

(2) INFORMATION FOR SEQ ID NO: 62:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 14)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:
GCGGCGGCAG CGCGG 15

(2) INFORMATION FOR SEQ ID NO: 63:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 62
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:
CCGCGCTGCC GCCGC 15

(2) INFORMATION FOR SEQ ID NO: 64:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 15)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:
CGGCGGGGCG ACGGA 15

(2) INFORMATION FOR SEQ ID NO: 65:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 64
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

TCCGTCGCCC CGCCG 15

(2) INFORMATION FOR SEQ ID NO: 66:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl-2 mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 16)
(I) FILING DATE: 20-SEP-1994
(J) PUBLICATION DATE: 30-MAR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:
CGGGAGCGCG GCGGGC 16

(2) INFORMATION FOR SEQ ID NO: 67:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 66
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:
GCCCGCCGCG CTCCCG 16

(2) INFORMATION FOR SEQ ID NO: 68:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to bcl-2 mRNA; a.k.a. "BCL-2"

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/08350 (SEQ ID NO: 17)

(I) FILING DATE: 20-SEP-1994

(J) PUBLICATION DATE: 30-MAR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

TCTCCCAGCG TGCGCCAT 18

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 68

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

ATGGCGCACG CTGGGAGA 18

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to ζ-Protein Kinase C

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 93/20101 (SEQ ID NO: 14)

(I) FILING DATE: 02-APR-1993

(J) PUBLICATION DATE: 14-OCT-1993

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

GGTCCTGCTG GGCAT 15

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 70

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

ATGCCCAGCA GGACC 15

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to a-Protein Kinase C Gene; a.k.a. "ISIS 3521"

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/02069 (SEQ ID NO: 2)

(I) FILING DATE: 08-JUL-1994

(J) PUBLICATION DATE: 19-JAN-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

GTTCTCGCTG GTGAGTTTCA 20

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 72
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:
TGAAACTCAC CAGCGAGAAC 20

(2) INFORMATION FOR SEQ ID NO: 74:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to c-raf kinase Gene; a.k.a. "ISIS 5132"
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: US 5563255 (SEQ ID NO: 8)
(I) FILING DATE: 05-31-1994
(J) PUBLICATION DATE: 08-OCT-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:
TCCCGCCTGT GACATGCATT 20

(2) INFORMATION FOR SEQ ID NO: 75:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 74

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:
AATGCATGTC ACAGGCGGGA 20

(2) INFORMATION FOR SEQ ID NO: 76:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to bcl/abl mRNA
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 92/02641
(I) FILING DATE: 09-AUG-1991
(J) PUBLICATION DATE: 20-FEB-1992
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:
GGCGTTTTGA ACTCTGCTT 19

(2) INFORMATION FOR SEQ ID NO: 77:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 76
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:
AAGCAGAGTT CAAAACGCC 19

(2) INFORMATION FOR SEQ ID NO: 78:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 1)

(I) FILING DATE: 28-SEP-1994

(J) PUBLICATION DATE: 06-APR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

CCTCTCTGTT TAAAACTTTA TCCAT 25

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 78

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

ATGGATAAAG TTTTAAACAG AGAGG 25

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 2)

(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:
TTCATATCCT GAGTCATGTC G 21

(2) INFORMATION FOR SEQ ID NO: 81:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 80
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:
CGACATGACT CAGGATATGA A 21

(2) INFORMATION FOR SEQ ID NO: 82:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 3)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:
GTCCCAGCGC TACGACGGGC CAAA 24

(2) INFORMATION FOR SEQ ID NO: 83:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 82
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:
TTTGGCCCGT CGTAGCGCTG GGAC 24

(2) INFORMATION FOR SEQ ID NO: 84:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 4)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:
GTCCCAGCGC TAC 13

(2) INFORMATION FOR SEQ ID NO: 85:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse

complement of SEQ ID NO: 84

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

GTAGCGCTGG GAC 13

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 5)

(I) FILING DATE: 28-SEP-1994

(J) PUBLICATION DATE: 06-APR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

TACGACGGGC CAAA 14

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 86

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

TTTGGCCCGT CGTA 14

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 6)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:
GTCCCAGCGC TACGACGGGC C 21

(2) INFORMATION FOR SEQ ID NO: 89:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 88
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:
GGCCCGTCGT AGCGCTGGGA C 21

(2) INFORMATION FOR SEQ ID NO: 90:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 7)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:
GTCCCAGCGC TACGACGG 18

(2) INFORMATION FOR SEQ ID NO: 91:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 90
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:
CCGTCGTAGC GCTGGGAC 18

(2) INFORMATION FOR SEQ ID NO: 92:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 8)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:
GTCCCAGCGC TACGA 15

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 92

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

TCGTAGCGCT GGGAC 15

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 9)

(I) FILING DATE: 28-SEP-1994

(J) PUBLICATION DATE: 06-APR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

CCAGCGCTAC GACGGGCCAA A 21

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 94
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:
TTTGGCCCGT CGTAGCGCTG G 21

(2) INFORMATION FOR SEQ ID NO: 96:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 10)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:
GCGCTACGAC GGGCCAAA 18

(2) INFORMATION FOR SEQ ID NO: 97:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 96
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:
TTTGGCCCGT CGTAGCGC 18

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta/A4 peptide
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 11)
(I) FILING DATE: 28-SEP-1994
(J) PUBLICATION DATE: 06-APR-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:
CTACGACGGG CCAAA 15

(2) INFORMATION FOR SEQ ID NO: 99:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 98
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:
TTTGGCCCGT CGTAG 15

(2) INFORMATION FOR SEQ ID NO: 100:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta/A4 peptide

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/09236 (SEQ ID NO: 15)

(I) FILING DATE: 28-SEP-1994

(J) PUBLICATION DATE: 06-APR-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

AAACCGGGCA GCATCGCGAC CCTG 24

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 100

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

CAGGGTCGCG ATGCTGCCCG GTTT 24

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to beta-globin; a.k.a. "5'ss"

(x) PUBLICATION INFORMATION:

(A) AUTHORS: Sierakowska, H., et al.

(B) TITLE: Repair of thalassemic human b-globin in mammalian cells by antisense oligonucleotides

(C) JOURNAL: The Proceedings of the National

Academy of Sciences (U.S.A.)
(D) VOLUME: 93
(F) PAGES: 12840-12844
(G) DATE: 12-NOV-1996

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:
GCUAUUACCU UAACCCAG 18

(2) INFORMATION FOR SEQ ID NO: 103:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 102
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:
CTGGGTTAAG GTAATAGC 18

(2) INFORMATION FOR SEQ ID NO: 104:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to beta-globin; a.k.a. "3'ss"
(x) PUBLICATION INFORMATION:
(A) AUTHORS: Sierakowska, H., et al.
(B) TITLE: Repair of thalassemic human b-globin in mammalian cells by antisense oligonucleotides
(C) JOURNAL: The Proceedings of the National Academy of Sciences (U.S.A.)
(D) VOLUME: 93

(F) PAGES: 12840-12844
(G) DATE: 12-NOV-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:
CAUUAUUGCC CUGAAAG 17

(2) INFORMATION FOR SEQ ID NO: 105:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 104
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:
CTTTCAGGGC AATAATG 17

(2) INFORMATION FOR SEQ ID NO: 106:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Multi-drug Resistance-1 (MDR-1) gene
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02556 (SEQ ID NO: 1)
(I) FILING DATE: 18-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:
TGTGCTCTTC CCACAGCCAC TG 22

(2) INFORMATION FOR SEQ ID NO: 107:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 106
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:
CAGTGGCTGT GGGAAGAGCA CA 22

(2) INFORMATION FOR SEQ ID NO: 108:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Multi-drug Resistance-1 (MDR-1) gene
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02556 (SEQ ID NO: 2)
(I) FILING DATE: 18-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:
TGTGCTCTTC CCACAGCCAC 20

(2) INFORMATION FOR SEQ ID NO: 109:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse

complement of SEQ ID NO: 108

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

GTGGCTGTGG GAAGAGCACA 20

(2) INFORMATION FOR SEQ ID NO: 110:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to Multi-drug Resistance-1 (MDR-1) gene

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 96/02556 (SEQ ID NO: 3)

(I) FILING DATE: 18-JUL-1995

(J) PUBLICATION DATE: 01-FEB-1996

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

GTGCTCTTCC CACAGCCACT 20

(2) INFORMATION FOR SEQ ID NO: 111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 110

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

AGTGGCTGTG GGAAGAGCAC 20

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Multi-drug Resistance-1 (MDR-1) gene
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02556 (SEQ ID NO: 4)
(I) FILING DATE: 18-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:
TGCTCTTCCC ACAGCCACTG 20

(2) INFORMATION FOR SEQ ID NO: 113:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 112
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:
CAGTGGCTGT GGGAAGAGCA 20

(2) INFORMATION FOR SEQ ID NO: 114:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to malarial agents; a.k.a. "PSI"

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 93/13740
(I) FILING DATE: 31-DEC-1991
(J) PUBLICATION DATE: 22-JUL-1993
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:
TAAAAAGAAT ATGATCTTCA T 21

(2) INFORMATION FOR SEQ ID NO: 115:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 114
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:
ATGAAGATCA TATTCTTTTT A 21

(2) INFORMATION FOR SEQ ID NO: 116:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to malarial agents; a.k.a. "PSII"
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 93/13740 (SEQ ID NO: PSII)
(I) FILING DATE: 31-DEC-1991
(J) PUBLICATION DATE: 22-JUL-1993
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:
AGCAACTGAG CCACCTGA 18

(2) INFORMATION FOR SEQ ID NO: 117:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 116
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:
TCAGGTGGCT CAGTTGCT 18

(2) INFORMATION FOR SEQ ID NO: 118:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to malarial agents; a.k.a. "PSIII"
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 93/13740
(I) FILING DATE: 31-DEC-1991
(J) PUBLICATION DATE: 22-JUL-1993
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:
GTCGCAGACT TGTTCCATCA T 21

(2) INFORMATION FOR SEQ ID NO: 119:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No

(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 118
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:
ATGATGGAAC AAGTCTGCGA C 21

(2) INFORMATION FOR SEQ ID NO: 120:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to malarial agents; a.k.a. "RI"
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 93/13740
(I) FILING DATE: 31-DEC-1991
(J) PUBLICATION DATE: 22-JUL-1993
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:
CTTGGCAGCT GCGCGTGACA T 21

(2) INFORMATION FOR SEQ ID NO: 121:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 120
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:
ATGTCACGCG CAGCTGCCAA G 21

(2) INFORMATION FOR SEQ ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to scistosome worms
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/33759 (SEQ ID NO: 1)
(I) FILING DATE: 30-MAY-1995
(J) PUBLICATION DATE: 14-DEC-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:
GCCATAGGGG GCAGGGAAGG C 21

(2) INFORMATION FOR SEQ ID NO: 123:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 122
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:
GCCTTCCCTG CCCCCCTATGG C 21

(2) INFORMATION FOR SEQ ID NO: 124:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HTLV-III

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: A)

(I) FILING DATE: 22-MAY-1987

(J) PUBLICATION DATE: 03-DEC-1987

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

CTGCTAGAGA TT 12

(2) INFORMATION FOR SEQ ID NO: 125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 124

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

AATCTCTAGC AG 12

(2) INFORMATION FOR SEQ ID NO: 126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HTLV-III

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: B)

(I) FILING DATE: 22-MAY-1987

(J) PUBLICATION DATE: 03-DEC-1987

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

CTGCTAGAGA TTTTCCACAC 20

(2) INFORMATION FOR SEQ ID NO: 127:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 126
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:
GTGTGGAAAA TCTCTAGCAG 20

(2) INFORMATION FOR SEQ ID NO: 128:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HTLV-III
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: C)
(I) FILING DATE: 22-MAY-1987
(J) PUBLICATION DATE: 03-DEC-1987
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:
TTCAAGTCCC TGTTCGGGCG CCAAA 25

(2) INFORMATION FOR SEQ ID NO: 129:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 128

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:
TTTGGCGCCC GAACAGGGAC TTGAA 25

(2) INFORMATION FOR SEQ ID NO: 130:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HTLV-III
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: D)
(I) FILING DATE: 22-MAY-1987
(J) PUBLICATION DATE: 03-DEC-1987
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:
GCGTACTCAC CAGTCGCCGC 20

(2) INFORMATION FOR SEQ ID NO: 131:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 130
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:
GCGGCGACTG GTGAGTACGC 20

(2) INFORMATION FOR SEQ ID NO: 132:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HTLV-III
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: E)
(I) FILING DATE: 22-MAY-1987
(J) PUBLICATION DATE: 03-DEC-1987
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:
CTGCTAGAGA TTAA 14

(2) INFORMATION FOR SEQ ID NO: 133:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 132
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:
TTAATCTCTA GCAG 14

(2) INFORMATION FOR SEQ ID NO: 134:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HTLV-III
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 87/07300 (SEQ ID NO: F)

(I) FILING DATE: 22-MAY-1987
(J) PUBLICATION DATE: 03-DEC-1987
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:
ACACCCAATT CTGAAAATGG 20

(2) INFORMATION FOR SEQ ID NO: 135:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 134
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:
CCATTTTCAG AATTGGGTGT 20

(2) INFORMATION FOR SEQ ID NO: 136:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(A) AUTHORS: Agrawal, Sudhir Tang, Jin Yan
(B) TITLE: GEM 91-An Antisense Oligonucleotide Phosphorothioate as a Therapeutic Agent for AIDS
(C) JOURNAL: Antisense Research and Development
(D) VOLUME: 2
(E) ISSUE: 6
(F) PAGES: 261-266
(G) DATE: Winter-1992
(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 1)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:
CTCTCGCACC CATCTCTCTC CTTCT 25

(2) INFORMATION FOR SEQ ID NO: 137:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 136
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:
AGAAGGAGAG AGATGGGTGC GAGAG 25

(2) INFORMATION FOR SEQ ID NO: 138:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 2)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:
CTCTCGCACC CATCTCTCTC CTTCTA 26

(2) INFORMATION FOR SEQ ID NO: 139:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 138
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:
TAGAAGGAGA GAGATGGGTG CGAGAG 26

(2) INFORMATION FOR SEQ ID NO: 140:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 3)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:
GCTCTCGCAC CCATCTCTCT CCTTCT 26

(2) INFORMATION FOR SEQ ID NO: 141:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 140

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:
AGAAGGAGAG AGATGGGTGC GAGAGC 26

(2) INFORMATION FOR SEQ ID NO: 142:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 4)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:
GCTCTCGCAC CCATCTCTCT CCTTCTA 27

(2) INFORMATION FOR SEQ ID NO: 143:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 142
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:
TAGAAGGAGA GAGATGGGTG CGAGAGC 27

(2) INFORMATION FOR SEQ ID NO: 144:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 5)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:
GCTCTCGCAC CCATCTCTCT CCTTCTAG 28

(2) INFORMATION FOR SEQ ID NO: 145:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 144
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:
CTAGAAGGAG AGAGATGGGT GCGAGAGC 28

(2) INFORMATION FOR SEQ ID NO: 146:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 6)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:
CGCTCTCGCA CCCATCTCTC TCCTTCTA 28

(2) INFORMATION FOR SEQ ID NO: 147:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 146
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:
TAGAAGGAGA GAGATGGGTG CGAGAGCG 28

(2) INFORMATION FOR SEQ ID NO: 148:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 7)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:
CGCTCTCGCA CCCATCTCTC TCCTTCTAG 29

(2) INFORMATION FOR SEQ ID NO: 149:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 148

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

CTAGAAGGAG AGAGATGGGT GCGAGAGCG 29

(2) INFORMATION FOR SEQ ID NO: 150:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV-1

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 8)

(I) FILING DATE: 04-OCT-1993

(J) PUBLICATION DATE: 14-APR-1994

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

CGCTCTCGCA CCCATCTCTC TCCTTCTAGC 30

(2) INFORMATION FOR SEQ ID NO: 151:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 150

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

GCTAGAAGGA GAGAGATGGG TGCGAGAGCG 30

(2) INFORMATION FOR SEQ ID NO: 152:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV-1
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 9)
(I) FILING DATE: 04-OCT-1993
(J) PUBLICATION DATE: 14-APR-1994
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:
ACGCTCTCGC ACCCATCTCT CTCCTTCTAG 30

(2) INFORMATION FOR SEQ ID NO: 153:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 152
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:
CTAGAAGGAG AGAGATGGGT GCGAGAGCGT 30

(2) INFORMATION FOR SEQ ID NO: 154
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV-1

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 94/08004 (SEQ ID NO: 10)

(I) FILING DATE: 04-OCT-1993

(J) PUBLICATION DATE: 14-APR-1994

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

CTCGCACCCA TCTCTCTCCT 20

(2) INFORMATION FOR SEQ ID NO: 155:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 154

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

AGGAGAGAGA TGGGTGCGAG 20

(2) INFORMATION FOR SEQ ID NO: 156:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV-1; a.k.a. "AR 177"

(x) PUBLICATION INFORMATION:

(A) AUTHORS: Bishop, J.S., et al.

(B) TITLE: Intramolecular G-quartet Motifs Confer Nuclease Resistance to a Potent Anti-HIV Oligonucleotide

(C) JOURNAL: The Journal of Biological Chemistry

(D) VOLUME: 271
(E) ISSUE: 10
(F) PAGES: 5698-5703
(G) DATE: 08-MAR-1996

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:
GTGGTGGGTG GGTGGGT 17

(2) INFORMATION FOR SEQ ID NO: 157:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 156
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:
ACCCACCCAC CCACCAC 17

(2) INFORMATION FOR SEQ ID NO: 158:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:
GCCTATTCTG CTATGTCGAC ACCCAA 26

(2) INFORMATION FOR SEQ ID NO: 159:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 158

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/03407 (SEQ ID NO: 94)

(I) FILING DATE: 19-JUL-1994

(J) PUBLICATION DATE: 02-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

UUGGGUGUCG ACAUAGCAGA AUAGGC 26

(2) INFORMATION FOR SEQ ID NO: 160:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

CTTCGGGCCT GTCGGGTCCC CTCGGG 26

(2) INFORMATION FOR SEQ ID NO: 161:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 160

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/03407

(I) FILING DATE: 19-JUL-1994

(J) PUBLICATION DATE: 02-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

CCCGAGGGGA CCCGACAGGC CCGAAG 26

(2) INFORMATION FOR SEQ ID NO: 162:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/03407

(I) FILING DATE: 19-JUL-1994

(J) PUBLICATION DATE: 02-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

CTTCGGGCCT GTCGGGTCCC CTCGGG 26

(2) INFORMATION FOR SEQ ID NO: 163:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 162

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

CCCGAGGGGA CCCGACAGGC CCGAAG 26

(2) INFORMATION FOR SEQ ID NO: 164:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 3)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:
GCTGGTGATC CTTTCCATCC CTGTGG 26

(2) INFORMATION FOR SEQ ID NO: 165:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 164
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:
CCACAGGGAT GGAAAGGATC ACCAGC 26

(2) INFORMATION FOR SEQ ID NO: 166:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 5)
(I) FILING DATE: 14-JUL-1995

(J) PUBLICATION DATE: 01-FEB-1996

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

CTACTACTCC TTGACTTTGG GGATTG 26

(2) INFORMATION FOR SEQ ID NO: 167:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 166

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

CAATCCCCAA AGTCAAGGAG TAGTAG 26

(2) INFORMATION FOR SEQ ID NO: 168:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 6)

(I) FILING DATE: 14-JUL-1995

(J) PUBLICATION DATE: 01-FEB-1996

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

CCTCTGTTAG TAACATATCC TGCTTTTCC 29

(2) INFORMATION FOR SEQ ID NO: 169:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 168
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:
GGAAAAGCAG GATATGTTAC TAACAGAGG 29

(2) INFORMATION FOR SEQ ID NO: 170:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 8)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:
GGTTGCTTCC TTCCTCTCTG GTACCC 26

(2) INFORMATION FOR SEQ ID NO: 171:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 170
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:
GGGTACCAGA GAGGAAGGAA GCAACC 26

(2) INFORMATION FOR SEQ ID NO: 172:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 10)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:
CTAGCAGTGG CGCCCGAACA GGTTCGCCTG 30
TTCGGGCGCC A 41

(2) INFORMATION FOR SEQ ID NO: 173:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 172
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:
TGGCGCCCGA ACAGGCGAAC CTGTTCGGGC 30
GCCACTGCTA G 41

(2) INFORMATION FOR SEQ ID NO: 174:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 22)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:
CATCACCTGC CATCTGTTTT CCATAATCCC 30

(2) INFORMATION FOR SEQ ID NO: 175:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 174
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:
GGGATTATGG AAAACAGATG GCAGGTGATG 30

(2) INFORMATION FOR SEQ ID NO: 176:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 23)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

CCTGTCTACT TGCCACACAA TCATCACCTG C 31

(2) INFORMATION FOR SEQ ID NO: 177:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 176
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:
GCAGGTGATG ATTGTGTGGC AAGTAGACAG G 31

(2) INFORMATION FOR SEQ ID NO: 178:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 96/02557 (SEQ ID NO: 25)
(I) FILING DATE: 14-JUL-1995
(J) PUBLICATION DATE: 01-FEB-1996
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:
ACTATTGCTA TTATTATTGC TACTACTAAT 30

(2) INFORMATION FOR SEQ ID NO: 179:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 178

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

ATTAGTAGTA GCAATAATAA TAGCAATAGT 30

(2) INFORMATION FOR SEQ ID NO: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 1)

(I) FILING DATE: 19-JUL-1994

(J) PUBLICATION DATE: 02-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

CTTCGGGCCT GTCGGGTCCC CTCGGG 26

(2) INFORMATION FOR SEQ ID NO: 181:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 2)

(I) FILING DATE: 19-JUL-1994

(J) PUBLICATION DATE: 02-FEB-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: HIV:

CUUCGGGCCU GUCGGGUCC CUCGGG 30

(2) INFORMATION FOR SEQ ID NO: 182:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NOS: 180 and 181
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:
CCCGAGGGGA CCCGACAGGC CCGAAG 26

(2) INFORMATION FOR SEQ ID NO: 183:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 3)
(I) FILING DATE: 19-JUL-1994
(J) PUBLICATION DATE: 02-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:
GCCTGTCGGG TCCC 14

(2) INFORMATION FOR SEQ ID NO: 184:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 4)
(I) FILING DATE: 19-JUL-1994
(J) PUBLICATION DATE: 02-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:
GCCUGUCGGG UCCC 14

(2) INFORMATION FOR SEQ ID NO: 185:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NOS: 183 snd 184
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:
GGGACCCGAC AGGC 14

(2) INFORMATION FOR SEQ ID NO: 186:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 186:
CTTCGGGCCT GTCGGGTCCC CTCGGG 26

(2) INFORMATION FOR SEQ ID NO: 187:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 186
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 5)
(I) FILING DATE: 19-JUL-1994
(J) PUBLICATION DATE: 02-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187:
CCCGAGGGGA CCCGACAGGC CCGAAG 26

(2) INFORMATION FOR SEQ ID NO: 188:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to HIV
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/03406 (SEQ ID NO: 6)
(I) FILING DATE: 19-JUL-1994
(J) PUBLICATION DATE: 02-FEB-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 188:
GCTGGTGATC CTTTCCATCC CTGTGG 26

(2) INFORMATION FOR SEQ ID NO: 189:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 188

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

CCACAGGGAT GGAAAGGATC ACCAGC 26

(2) INFORMATION FOR SEQ ID NO: 190:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to HIV; a.k.a. "ISIS 5320"

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: US 5523389

(I) FILING DATE: 28-SEP-1994

(J) PUBLICATION DATE: 04-JUN-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

TTGGGGTT 8

(2) INFORMATION FOR SEQ ID NO: 191:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 190

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

AACCCCAA 8

(2) INFORMATION FOR SEQ ID NO: 192:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to influenza virus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 1)

(I) FILING DATE: 29-APR-1991

(J) PUBLICATION DATE: 14-NOV-1991

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

CATTCAAATG GTTTGCCTGC 20

(2) INFORMATION FOR SEQ ID NO: 193:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 192

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

GCAGGCAAAC CATTTGAATG 20

(2) INFORMATION FOR SEQ ID NO: 194:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 2)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 194:
GCAGGCAAAC CATTTGAATG 20

(2) INFORMATION FOR SEQ ID NO: 195:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 194
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195:
CATTCAAATG GTTTGCCTGC 20

(2) INFORMATION FOR SEQ ID NO: 196:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 3)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 196:
CCATAATCCC CTGCTTCTGC 20

(2) INFORMATION FOR SEQ ID NO: 197:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 196
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:
GCAGAAGCAG GGGATTATGG 20

(2) INFORMATION FOR SEQ ID NO: 198:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 4)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:
GCAGAAGCAG GGGATTATGG 20

(2) INFORMATION FOR SEQ ID NO: 199:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 198
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:
CCATAATCCC CTGCTTCTGC 20

(2) INFORMATION FOR SEQ ID NO: 200:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 5)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 200:
GCAGAAGCAG AGGATTATGG 20

(2) INFORMATION FOR SEQ ID NO: 201:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 200
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

CCATAATCCT CTGCTTCTGC 20

(2) INFORMATION FOR SEQ ID NO: 202:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 6)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:
GCATAAGCAG AGGATCATGG 20

(2) INFORMATION FOR SEQ ID NO: 203:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 202
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 203:
CCATGATCCT CTGCTTATGC 20

(2) INFORMATION FOR SEQ ID NO: 204:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to influenza virus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 7)

(I) FILING DATE: 29-APR-1991

(J) PUBLICATION DATE: 14-NOV-1991

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

GGCAAGCTTT ATTGAGGCTT 20

(2) INFORMATION FOR SEQ ID NO: 205:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 204

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

AAGCCTCAAT AAAGCTTGCC 20

(2) INFORMATION FOR SEQ ID NO: 206:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to influenza virus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 8)

(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:
ATCTTCATCA TCTGAGAGAT 20

(2) INFORMATION FOR SEQ ID NO: 207:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 206
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 207:
ATCTCTCAGA TGATGAAGAT 20

(2) INFORMATION FOR SEQ ID NO: 208:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to influenza virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 91/16902 (SEQ ID NO: 9)
(I) FILING DATE: 29-APR-1991
(J) PUBLICATION DATE: 14-NOV-1991
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:
CGTAAGCAAC AGTAGTCCTA 20

(2) INFORMATION FOR SEQ ID NO: 209:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 208
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 209:
TAGGACTACT GTTGCTTACG 20

(2) INFORMATION FOR SEQ ID NO: 210:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus intron-exon boundary of genes UL36 and UL37; a.k.a. "UL36ANTI" and "GEM 132"
(x) PUBLICATION INFORMATION:
(A) AUTHORS: Pari, G.S., et al.
(B) TITLE: Potent Antiviral Activity of an Antisense Oligonucleotide Complementary to the Intron-Exon Boundary of Human Cytomegalovirus Genes UL36 and UL37
(C) JOURNAL: Antimicrobial Agents and Chemotherapy
(D) VOLUME: 39
(E) ISSUE: 5
(F) PAGES: 1157-1161
(G) DATE: MAY-1995
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 1)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 210:
TGGGGCTTAC CTTGCGAACA 20

(2) INFORMATION FOR SEQ ID NO: 211:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 210
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:
TGTTCGCAAG GTAAGCCCCA 20

(2) INFORMATION FOR SEQ ID NO: 212:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 2)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:
GACGTGGGGC TTACCTTGCG 20

(2) INFORMATION FOR SEQ ID NO: 213:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 212
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 213:
CGCAAGGTAA GCCCCACGTC 20

(2) INFORMATION FOR SEQ ID NO: 214:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 3)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:
TCTTCAACGA CGTGGGGCTT 20

(2) INFORMATION FOR SEQ ID NO: 215:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 214
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

AAGCCCCACG TCGTTGAAGA 20

(2) INFORMATION FOR SEQ ID NO: 216:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 4)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:
GACGCGTGGC ATGCTTGGTG T 21

(2) INFORMATION FOR SEQ ID NO: 217:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 216
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:
ACACCAAGCA TGCCACGCGT C 21

(2) INFORMATION FOR SEQ ID NO: 218:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 5)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:
AGGTTGGGGT CGACGCGTGG C 21

(2) INFORMATION FOR SEQ ID NO: 219:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 218
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:
GCCACGCGTC GACCCCAACC T 21

(2) INFORMATION FOR SEQ ID NO: 220:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 6)

(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:
GGCTGAGCGG TCATCCTCGG A 21

(2) INFORMATION FOR SEQ ID NO: 221:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 220
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:
TCCGAGGATG ACCGCTCAGC C 21

(2) INFORMATION FOR SEQ ID NO: 222:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 7)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:
CGGGACTCAC CGTCGTTCTG 20

(2) INFORMATION FOR SEQ ID NO: 223:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 222
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 223:
CAGAACGACG GTGAGTCCCG 20

(2) INFORMATION FOR SEQ ID NO: 224:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to cytomagalovirus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 8)
(I) FILING DATE: 19-MAY-1995
(J) PUBLICATION DATE: 30-NOV-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:
GGAGGAGAGC CTACAGACGG 20

(2) INFORMATION FOR SEQ ID NO: 225:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse

complement of SEQ ID NO: 224

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

CCGTCTGTAG GCTCTCCTCC 20

(2) INFORMATION FOR SEQ ID NO: 226:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to cytomagalovirus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/32213 (SEQ ID NO: 9)

(I) FILING DATE: 19-MAY-1995

(J) PUBLICATION DATE: 30-NOV-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

AGTAACGCAC CGTCGGTGCC 20

(2) INFORMATION FOR SEQ ID NO: 227:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 226

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

GGCACCGACG GTGCGTTACT 20

(2) INFORMATION FOR SEQ ID NO: 228:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Epstein-Barr Virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22554 (SEQ ID NO: 1)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:
TTTGGGTCCA TCATCTTCAG CAAAG 25

(2) INFORMATION FOR SEQ ID NO: 229:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 228
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:
CTTTGCTGAA GATGATGGAC CCAAA 25

(2) INFORMATION FOR SEQ ID NO: 230:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Epstein-Barr Virus

(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22554 (SEQ ID NO: 2)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 230:
CATCATCTTC AGCAAAGATA 20

(2) INFORMATION FOR SEQ ID NO: 231:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 230
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 231:
TATCTTTGCT GAAGATGATG 20

(2) INFORMATION FOR SEQ ID NO: 232:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Epstein-Barr Virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22554 (SEQ ID NO: 3)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 232:
TCAGAAGTCG AGTTTGGGTC 20

(2) INFORMATION FOR SEQ ID NO: 233:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 232
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 233:
GACCCAAACT CGACTTCTGA 20

(2) INFORMATION FOR SEQ ID NO: 234:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Respiratory Syncytial Virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22553 (SEQ ID NO: 1)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 234:
ACGCGAAAAA ATGCGTACAA 20

(2) INFORMATION FOR SEQ ID NO: 235:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No

(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 234
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 235:
TTGTACGCAT TTTTTCGCGT 20

(2) INFORMATION FOR SEQ ID NO: 236:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Respiratory Syncytial Virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22553 (SEQ ID NO: 2)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 236:
TAAACCAAAA AAATGGGGCA 20

(2) INFORMATION FOR SEQ ID NO: 237:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 236
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 237:
TGCCCCATTT TTTTGGTTTA 20

(2) INFORMATION FOR SEQ ID NO: 238:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:
(D) OTHER INFORMATION: Antisense to Respiratory Syncytial Virus
(x) PUBLICATION INFORMATION:
(H) DOCUMENT NUMBER: WO 95/22553 (SEQ ID NO: 3)
(I) FILING DATE: 17-FEB-1995
(J) PUBLICATION DATE: 24-AUG-1995
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 238:
AAATGGGGCA AATAAGAATT 20

(2) INFORMATION FOR SEQ ID NO: 239:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: No
(ix) FEATURE:
(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 238
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 239:
AATTCTTATT TGCCCCATTT 20

(2) INFORMATION FOR SEQ ID NO: 240:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear
(iv) ANTI-SENSE: Yes
(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to Respiratory Syncytial Virus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: WO 95/22553 (SEQ ID NO: 4)

(I) FILING DATE: 17-FEB-1995

(J) PUBLICATION DATE: 24-AUG-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 240:

AAAAATGGGG CAAATAAATC 20

(2) INFORMATION FOR SEQ ID NO: 241:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 240

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 241:

GATTTATTTG CCCCATTTTT 20

(2) INFORMATION FOR SEQ ID NO: 242:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: Yes

(ix) FEATURE:

(D) OTHER INFORMATION: Antisense to cytomegalovirus

(x) PUBLICATION INFORMATION:

(H) DOCUMENT NUMBER: US 5442049 (SEQ ID NO: 22)

(I) FILING DATE: 25-JAN-1993

(J) PUBLICATION DATE: 15-AUG-1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 242:

GCGTTTGCTC TTCTTCTTGC G 21

(2) INFORMATION FOR SEQ ID NO: 243:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: Nucleic Acid

(C) STRANDEDNESS: Single

(D) TOPOLOGY: Linear

(iv) ANTI-SENSE: No

(ix) FEATURE:

(D) OTHER INFORMATION: Full-length reverse complement of SEQ ID NO: 242

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 243:

CGCAAGAAGA AGAGCAAACG C 21

What is claimed is:

1. A matrix comprising a support and an affinity unit, wherein said affinity unit specifically and reversibly binds a target oligonucleotide, and wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide.

2. The matrix of claim 1 further comprising a linker.

3. The matrix of claim 1 further comprising a spacer.

4. The matrix of claim 1 further comprising a spacer and a linker.

5. The matrix of claim 1 wherein said support is a solid support.

6. The matrix of claim 1 wherein said support is a soluble support.

7. The matrix of claim 1 wherein said affinity unit is synthesized *in situ*.

8. The matrix of claim 1 wherein said affinity unit is synthesized independently from said support and subsequently attached to said support.

9. The matrix of claim 1 wherein said affinity unit comprises at least one modified nucleobase.

10. The matrix of claim 9, wherein said modified nucleobase is selected from the group consisting of 5-methyl cytosine, uridine 5-propynyl methylthiazole, thymidine 5-propynyl methylthiazole, uridine 5-amino-ethyl-3-acrylimido, thymidine 5-amino-ethyl-3-acylimido, 2-thio uridine, 2-thio

thymidine, a 7-modified-7-deaza purine, and 2-amino-adenosine.

11. A matrix comprising a support and an affinity unit, wherein said affinity unit specifically and reversibly binds a target oligonucleotide, wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide, and wherein said affinity unit comprises at least one modified sugar residue.

12. The matrix of claim 11, wherein said modified sugar residue is a 4'-6' methano carbocyclic derivative.

13. The matrix of claim 11, wherein said modified sugar residue is a ribose residue comprising a 2' modification.

14. The matrix of claim 13, wherein said 2' modification is selected from the group consisting of 2'-fluoro; 2'-O-'alkyl; 2'-O-allyl; 2'-O-butyl; 2'-O-methyl; 2'-O-methoxy-ethyl; 2'-O-alkoxy-alkoxy; 2'-O-aminoalkyl; an intercalating agent linked to the 2' position; and 2'-O-CH_2-CHR-X, where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3.

15. The matrix of claim 1 wherein said affinity unit comprises at least one modified backbone linkage.

16. The matrix of claim 15, wherein said modified backbone linkage is selected from the group consisting of a polyamide backbone linkage; a methylene(methylimino) backbone linkage; a dimethylhydrazino backbone linkage; an amide 3 backbone linkage; an amide 4 backbone linkage; a phosphoryl linked morpholino backbone linkage; a phosphonate backbone linkage; a formacetal/ketal type backbone linkage; an N3'->P5' phosphoramidite backbone linkage; and a backbone

linkage comprising 1,5-anhydrohexitol.

17. A matrix comprising a support and an affinity unit, wherein said affinity unit specifically and reversibly binds a target oligonucleotide, wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide, and wherein said affinity unit is or comprises a peptide nucleic acid.

18. The matrix of claim 1 wherein said affinity unit comprises at least one modified sugar residue and at least one modified nucleobase.

19. The matrix of claim 18, wherein said modified sugar residue is a 4'-6' methano carbocyclic derivative.

20. The matrix of claim 18, wherein said modified sugar residue is a ribose residue comprising a 2' modification.

21. The matrix of claim 20, wherein said 2' modification is selected from the group consisting of 2'-fluoro; 2'-O-'alkyl; 2'-O-allyl; 2'-O-butyl; 2'-O-methyl; 2'-O-methoxy-ethyl; 2'-O-alkoxy-alkoxy; 2'-O-aminoalkyl; an intercalating agent linked to the 2' position; and 2'-O-CH_2-CHR-X, where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3.

22. The matrix of claim 18, wherein said modified nucleobase is selected from the group consisting of 5-methyl cytosine, uridine 5-propynyl methylthiazole, thymidine 5-propynyl methylthiazole, uridine 5-amino-ethyl-3-acrylimido, thymidine 5-amino-ethyl-3-acrylimido, 2-thio uridine, 2-thio thymidine, a 7-modified-7-deaza purine, and 2-amino-adenosine.

23. The matrix of claim 1 wherein said affinity unit comprises at least one modified sugar residue and at least one modified backbone linkage.

24. The matrix of claim 23, wherein said modified sugar residue is a 4'-6' methano carbocyclic derivative.

25. The matrix of claim 23, wherein said modified sugar residue is a ribose residue comprising a 2' modification.

26. The matrix of claim 25, wherein said 2' modification is selected from the group consisting of 2'-fluoro; 2'-O-'alkyl; 2'-O-allyl; 2'-O-butyl; 2'-O-methyl; 2'-O-methoxy-ethyl; 2'-O-alkoxy-alkoxy; 2'-O-aminoalkyl; an intercalating agent linked to the 2' position; and 2'-O-CH_2-CHR-X, where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3.

27. The matrix of claim 23, wherein said modified backbone linkage is selected from the group consisting of a polyamide backbone linkage; a methylene(methylimino) backbone linkage; a dimethylhydrazino backbone linkage; an amide 3 backbone linkage; an amide 4 backbone linkage; a phosphoryl linked morpholino backbone linkage; a phosphonate backbone linkage; a formacetal/ketal type backbone linkage; an N3'->P5' phosphoramidite backbone linkage; and a backbone linkage comprising 1,5-anhydrohexitol.

28. The matrix of claim 1 wherein said affinity unit comprises at least one modified sugar residue, at least one modified backbone linkage, and at least one modified nucleobase.

29. The matrix of claim 1 wherein said affinity unit is RNA or RNA-like.

30. The matrix of claim 1 wherein said affinity unit comprises at least one modification selected from the group consisting of a modified sugar residue, a modified backbone linkage, and a modified nucleobase, wherein said modification enhances the affinity of the affinity unit for, and/or duplex stability of the affinity unit with, RNA and RNA-like molecules.

31. The matrix of claim 1 wherein said affinity unit comprises at least one modification selected from the group consisting of a modified sugar residue, a modified backbone linkage, and a modified nucleobase, wherein said modification results in said affinity unit having a capacity to form a stable duplex with an RNA or RNA-like molecule that exceeds its ability to form a stable duplex with a DNA molecule of the same sequence under comparable conditions.

32. The matrix of claim 1, wherein said affinity unit has a tendency to be organized to selectively bind complementary RNA or RNA-like molecules with high affinity and specificity.

33. The matrix of claim 1, wherein said affinity unit preferably forms an A-type helix with complementary RNA or RNA-like molecules.

34. The matrix of claim 1, wherein said affinity unit comprises a nucleobase sequence having from 5 to about 25 contiguous nucleobases derived from a sequence selected from the group consisting of SEQ ID NOS:2, 17, 19, 21, 23, 27, 29, 31, 33, 35, 37, 39, 41, 43, 25, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 182, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209,

211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241 and 243.

35. A matrix comprising a support and an affinity unit, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit:

(a) specifically and reversibly binds a target oligonucleotide, wherein said target oligonucleotide has a length, n, of from 5 to 50 nucleobases; and

(b) has a length, p, wherein p is a positive whole number ranging from 4 to n+4; and

(c) is, over said length p, the reverse complement of the nucleobase sequence of said target oligonucleotide, provided that, in a duplex between said target oligonucleotide and said nucleobase sequence of said affinity unit, neither a 5' overhang nor a 3' overhang of the duplex formed between said target oligonucleotide and said affinity unit is greater than two nucleobases.

36. A matrix comprising a support and an affinity unit, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit specifically and reversibly binds a target oligonucleotide, wherein said target oligonucleotide and said nucleobase sequence of said affinity unit each have a length, n, of from 5 to 50 nucleobases, and said nucleobase sequence of said affinity unit is the reverse complement of the nucleobase sequence of said target oligonucleotide.

37. A matrix comprising a support and an affinity unit, wherein said affinity unit specifically and reversibly binds a target oligonucleotide, wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide, and wherein said nucleobase sequence of said affinity unit is in the form of a polymer selected from

the group consisting of an oligodeoxyribonucleotide, an oligoribonucleotide, a chimeric oligonucleotide and an oligonucleotide having one or more modified linkages.

38. The matrix of claim 1, wherein said affinity unit selectively binds and retains said target oligonucleotide with high affinity and specificity under conditions wherein derivatives of said target oligonucleotide having one or more mismatches with the nucleobase sequence of said affinity unit are not bound and retained.

39. The matrix of claim 38, wherein said affinity unit has at least one modification selected from the group consisting of a modified sugar residue, a modified backbone linkage and a modified nucleobase.

40. The matrix of claim 38, wherein said affinity unit has two or more modification selected from the group consisting of a modified sugar residue, a modified backbone linkage and a modified nucleobase.

41. A method of purifying a synthetic target oligonucleotide from a mixture which comprises said target oligonucleotide and one or more undesired contaminants comprising contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker; wherein said affinity unit specifically and reversibly binds a target oligonucleotide; and wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide.

42. The method of claim 41 further comprising the step of dissociating said target oligonucleotide from said affinity unit and recovering said target oligonucleotide.

43. A method of purifying a synthetic target oligonucleotide from a mixture which comprises said target oligonucleotide and one or more undesired contaminants comprising contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker; wherein said affinity unit specifically and reversibly binds a target oligonucleotide; wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide; and wherein said nucleobase sequence of said affinity unit is at least partially in the form of a peptide nucleic acid.

44. The method of claim 43 further comprising the step of dissociating said target oligonucleotide from said affinity unit and recovering said target oligonucleotide.

45. The method of claim 44 wherein said dissociating of said target oligonucleotide from said affinity unit is achieved by the addition of ammonium hydroxide.

46. A method of purifying a synthetic target oligonucleotide from a mixture which comprises said target oligonucleotide and one or more undesired contaminants comprising contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit:

(a) specifically and reversibly binds a target oligonucleotide, wherein said target oligonucleotide has a length, n, of from 5 to 50 nucleobases; and

(b) has a length, p, wherein p is a positive whole number ranging from 4 to n+4; and

(c) is, over said length p, the reverse

complement of the nucleobase sequence of said target oligonucleotide, provided that, in a duplex between said target oligonucleotide and said nucleobase sequence of said affinity unit, neither a 5' overhang nor a 3' overhang of the duplex formed between said target oligonucleotide and said affinity unit is greater than two nucleobases.

47. A method of purifying a synthetic target oligonucleotide from a mixture which comprises said target oligonucleotide and one or more undesired contaminants comprising contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit specifically and reversibly binds a target oligonucleotide, wherein said target oligonucleotide and said nucleobase sequence of said affinity unit each have a length, n, of from 5 to 50 nucleobases, and said nucleobase sequence of said affinity unit is the reverse complement of the nucleobase sequence of said target oligonucleotide.

48. A method of purifying a synthetic target oligonucleotide from a mixture comprising said target oligonucleotide and one or more undesired contaminants, comprising the steps of:

(a) contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said affinity unit specifically and reversibly binds a target oligonucleotide, and wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a portion of said target oligonucleotide;

(b) removing said undesired contaminants of said

target oligonucleotide; and

(c) dissociating said target oligonucleotide from said matrix and recovering said dissociated target oligonucleotide.

49. A method of purifying a synthetic target oligonucleotide from a mixture comprising said target oligonucleotide and one or more undesired contaminants, comprising the steps of:

(a) contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit:

(1) specifically and reversibly binds a target oligonucleotide, wherein said target oligonucleotide has a length, n, of from 5 to 50 nucleobases;

(2) has a length, p, wherein p is a positive whole number ranging from 4 to n+4; and

(3) is, over said length p, the reverse complement of the nucleobase sequence of said target oligonucleotide, provided that, in a duplex between said target oligonucleotide and said nucleobase sequence of said affinity unit, neither a 5′ overhang nor a 3′ overhang of said target oligonucleotide is greater than two nucleobases;

(b) removing said undesired contaminants of said target oligonucleotide; and

(c) dissociating said target oligonucleotide from said matrix and recovering said dissociated target oligonucleotide.

50. A method of purifying a synthetic target oligonucleotide from a mixture comprising said target oligonucleotide and one or more undesired contaminants, comprising the steps of:

(a) contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said affinity unit comprises a nucleobase sequence, wherein said nucleobase sequence of said affinity unit specifically and reversibly binds said target oligonucleotide, wherein said target oligonucleotide and said nucleobase sequence of said affinity unit each have a length, n, of from 5 to 50 nucleobases, and wherein said nucleobase sequence of said affinity unit is the reverse complement of the nucleobase sequence of said target oligonucleotide;

(b) removing said undesired contaminants of said target oligonucleotide; and

(c) dissociating said target oligonucleotide from said matrix and recovering said dissociated target oligonucleotide.

51. The method of claim 50, wherein said step (b) is achieved by washing said matrix.

52. The method of claim 50, wherein said step (b) is achieved by isocratic, gradient or step-gradient washing using appropriate buffers such that said washing begins at a pH of about 5 and concludes at a pH of about 10.

53. The method of claim 50, wherein said contaminant removing step (b) is performed at a temperature which is at least 1°C below the T_m of the duplex composed of said nucleobase sequence of said affinity unit hybridized to said

target oligonucleotide.

54. The method of claim 50, wherein said dissociation and recovery step (c) is achieved by washing said matrix with distilled water and collecting the resultant eluent.

55. A method of purifying a synthetic target oligonucleotide from a first mixture comprising said target oligonucleotide and one or more undesired contaminants, comprising the steps of contacting said first mixture to a first matrix, wherein said first matrix comprises a support and a first affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said first affinity unit comprises a nucleobase sequence having the reverse complement of a first hybridizing portion of said target oligonucleotide; dissociating and recovering oligonucleotide material bound to said matrix comprising said first affinity unit, to obtain a second mixture comprising said target oligonucleotide and one or more undesired contaminants bound by said first affinity unit; contacting said second mixture to a second matrix, wherein said second matrix comprises a support and a second affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker, wherein said second affinity unit comprises a nucleobase sequence having the reverse complement of a second hybridizing portion of said target oligonucleotide; dissociating and recovering oligonucleotide material bound to said second matrix comprising said second affinity unit, to obtain a third mixture comprising said target oligonucleotide; wherein said first and second hybridizing portions of said target oligonucleotide are distinct enough from one another such that different undesirable contaminating derivatives of the target oligonucleotide are removed by said first and said second matrix.

56. The method of claim 55, wherein said nucleobase

sequence of said affinity unit is in the form of a polymer selected from the group consisting of a peptide nucleic acid, an oligodeoxyribonucleotide, an oligoribonucleotide, a chimeric oligonucleotide and an oligonucleotide having one or more modified linkages.

57. The method of claim 55, wherein said one or more undesired contaminants comprises one or more deletion derivatives of said target oligonucleotide.

58. The method of claim 41, wherein said target oligonucleotide is a chimeric oligonucleotide.

59. The method of claim 41, wherein said target oligonucleotide is or comprises a peptide nucleic acid.

60. A method of purifying a synthetic target oligonucleotide from a mixture which comprises said target oligonucleotide and one or more undesired contaminants comprising contacting said mixture with a matrix, wherein said matrix comprises a support and an affinity unit, and optionally comprises a linker, a spacer or a spacer and a linker; wherein said affinity unit specifically and reversibly binds a target oligonucleotide; wherein said affinity unit comprises a nucleobase sequence having the reverse complement of a hybridizing portion of said target oligonucleotide; and wherein said target oligonucleotide is an oligonucleotide designed to have antisense activity.

61. The method of claim 60, wherein said target oligonucleotide has an antisense sequence to a portion of a gene selected from the group consisting of *c-myb*, *bcl-2*, *bcl-abl*, *c-raf*, a gene encoding a protein kinase C, and a gene encoding a growth factor.

62. The method of claim 61, wherein said target oligonucleotide is an oligonucleotide designed to have

therapeutic activity against disorders resulting at least in part from hyperproliferative cells.

63. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a non-pathogenic and non-hyperproliferative disorder.

64. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to modulate the expression of a protein displayed on a cell surface.

65. The method of claim 64, wherein said protein selected on a cell surface is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3, VCAM, a B7 protein, and an MDR P-glycoprotein.

66. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a eukaryotic pathogen.

67. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a human retrovirus.

68. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a human immunodeficiency virus.

69. The method of claim 68, wherein said target oligonucleotide has an antisense sequence to a retroviral gene selected from the group consisting of *gag*, *tat*, *vpr*, *rev*, *env*, *nef* and *pol*.

70. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a virus other than a human

retrovirus.

71. The method of claim 70, wherein said virus other than a human retrovirus is selected from the group consisting of influenza virus, Epstein-Barr virus, Respiratory Syncytial Virus, and cytomegalovirus.

72. The method of claim 60, wherein said antisense oligonucleotide has an antisense sequence to a portion of a gene selected from the group consisting of *c-myb*, *bcl-2*, *bcl-abl*, *c-raf*, a gene encoding a protein kinase C, and a gene encoding a growth factor.

73. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against disorders resulting at least in part from hyperproliferative cells.

74. The method of claim 60, wherein said target oligonucleotide is an oligonucleotide designed to have therapeutic activity against a non-pathogenic and non-hyperproliferative disorder.

75. The method of claim 41, wherein said hybridizing portion of said target oligonucleotide is RNA or RNA-like, and said affinity unit comprises at least one of the following modifications: at least one modified sugar residue, at least one modified backbone linkage, or a modified nucleobase.

76. The method of claim 75, wherein said affinity unit comprises at least one ribose residue comprising a 2' modification.

77. The method of claim 76, wherein said 2' modification is selected from the group consisting of 2'-fluoro; 2'-O-'alkyl; 2'-O-allyl; 2'-O-butyl; 2'-O-methyl;

2'-O-methoxy-ethyl; 2'-O-alkoxy-alkoxy; 2'-O-aminoalkyl; an intercalating agent linked to the 2' position; and 2'-O-CH_2-CHR-X, where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3.

78. The method of claim 75, wherein said affinity unit comprises at least one modified backbone linkage, wherein said modified backbone linkage is selected from the group consisting of a polyamide backbone linkage; a methylene(methylimino) backbone linkage; a dimethylhydrazino backbone linkage; an amide 3 backbone linkage; an amide 4 backbone linkage; a phosphoryl linked morpholino backbone linkage; a phosphonate backbone linkage; a formacetal/ketal type backbone linkage; an N3'->P5' phosphoramidite backbone linkage; and a backbone linkage comprising 1,5-anhydrohexitol.

79. The method of claim 75, wherein said affinity unit comprises at least one modified nucleobase, wherein said modified nucleobase is selected from the group consisting of 5-methyl cytosine, uridine 5-propynyl methylthiazole, thymidine 5-propynyl methylthiazole, uridine 5-amino-ethyl-3-acrylimido, thymidine 5-amino-ethyl-3-acrylimido, 2-thio uridine, 2-thio thymidine, a 7-modified-7-deaza purine, and 2-amino-adenosine.

80. The method of claim 75, wherein said affinity unit comprises at least two of the following elements:

(a) at least one modified backbone linkage selected from the group consisting of a polyamide backbone linkage; a methylene(methylimino) backbone linkage; a dimethylhydrazino backbone linkage; an amide 3 backbone linkage; an amide 4 backbone linkage; a phosphoryl linked morpholino backbone linkage; a phosphonate backbone linkage; a formacetal/ketal type backbone linkage; an N3'->P5' phosphoramidite backbone linkage; and a backbone linkage comprising 1,5-anhydrohexitol;

(b) at least one ribose residue comprising a 2' modification selected from the group consisting of 2'-fluoro, 2'-O-'alkyl, 2'-O-allyl, 2'-O-butyl, 2'-O-methyl, 2'-O-methoxy-ethyl, 2'-O-alkoxy-alkoxy, 2'-O-aminoalkyl, an intercalating agent linked to the 2' position, and 2'-O-CH_2-CHR-X, where X = OH, F, CF_3 or OCH_3 and R = H, CH_3, CH_2OH or CH_2OCH_3, and

(c) at least one modified nucleobase selected from the group consisting of 5-methyl cytosine, uridine 5-propynyl methylthiazole, thymidine 5-propynyl methylthiazole, uridine 5-amino-ethyl-3-acrylimido, thymidine 5-amino-ethyl-3-acrylimido, 2-thio uridine, 2-thio thymidine, a 7-modified-7-deaza purine, and 2-amino-adenosine.

81. The method of claim 41, wherein said hybridizing portion of said target oligonucleotide is RNA or RNA-like, and said affinity unit has a tendency to be organized to selectively bind complementary RNA or RNA-like molecules with high affinity and specificity.

82. The method of claim 41, wherein said hybridizing portion of said target oligonucleotide is RNA or RNA-like, and said affinity unit preferably forms an A-type helix with complementary RNA or RNA-like molecules.

83. The method of claim 41, wherein said target oligonucleotide comprises at least one ribose residue comprising a 2' modification, or at least one 5-methyl cytosine, in said hybridizing portion thereof, and said affinity unit comprises at least one of the following modifications: at least one modified sugar residue, at least one modified backbone linkage, or at least one modified nucleobase.

84. The method of claim 41, said affinity unit having at least one ribose residue comprising a 2' modification.

85. The method of claim 41, wherein said hybridizing portion of said target oligonucleotide comprises at least one of the following modifications: at least one modified sugar residue, at least one modified backbone linkage, or at least one modified nucleobase, and said affinity unit is RNA or RNA-like.

86. The method of claim 41 wherein said target oligonucleotide has been prepared by a blockwise synthesis procedure.

87. The method of claim 41 wherein said target oligonucleotide has been prepared by solution synthesis.

88. A target oligonucleotide enriched in purity by the method of claim 41.

89. A target oligonucleotide enriched in purity by the method of claim 43.

90. A target oligonucleotide designed to have antisense activity enriched in purity by the method of claim 60.

91. A target oligonucleotide comprising at least one ribose residue comprising a 2' modification or at least one 5-methyl cytosine enriched in purity by the method of claim 79.

92. A pharmaceutical composition comprising a target oligonucleotide enriched in purity by the method of claim 41.

93. A pharmaceutical composition comprising a target oligonucleotide enriched in purity by the method of claim 43.

94. A pharmaceutical composition comprising a target oligonucleotide designed to have antisense activity and enriched in purity by the method of claim 60.

95. A pharmaceutical composition comprising a target oligonucleotide enriched in purity by the method of claim 79, wherein said target oligonucleotide comprises at least one ribose residue comprising a 2' modification or at least one 5-methyl cytosine.

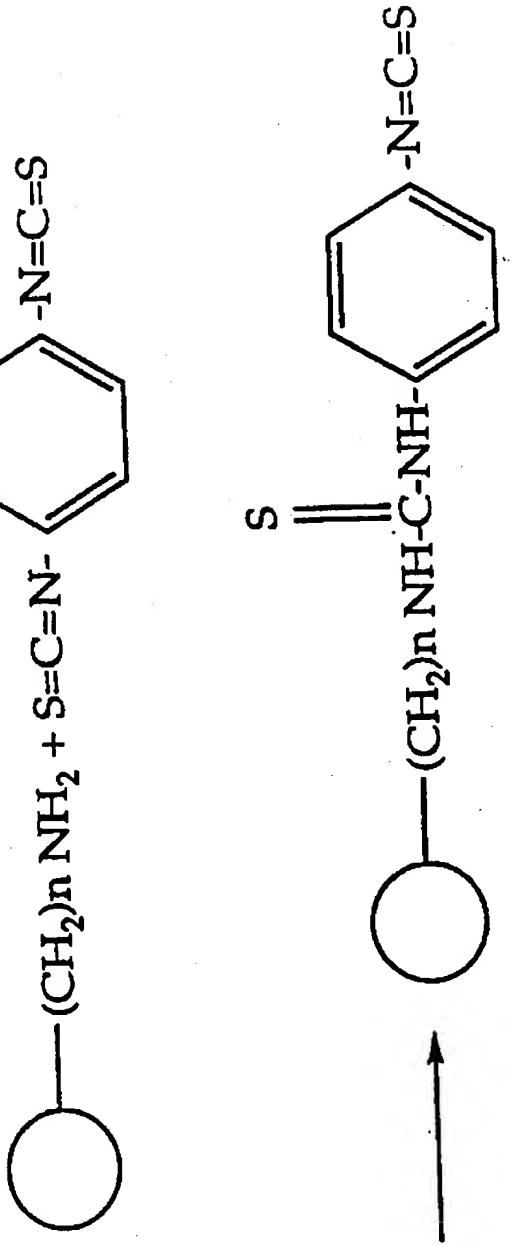

Figure 1

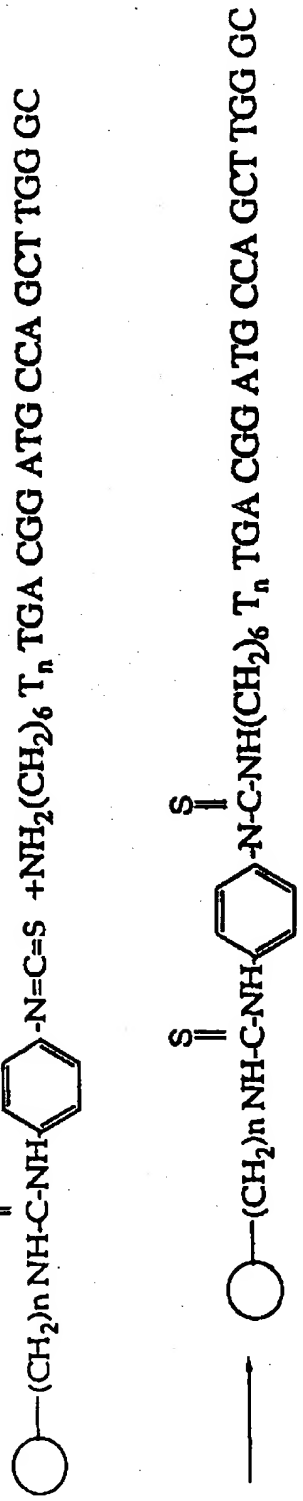
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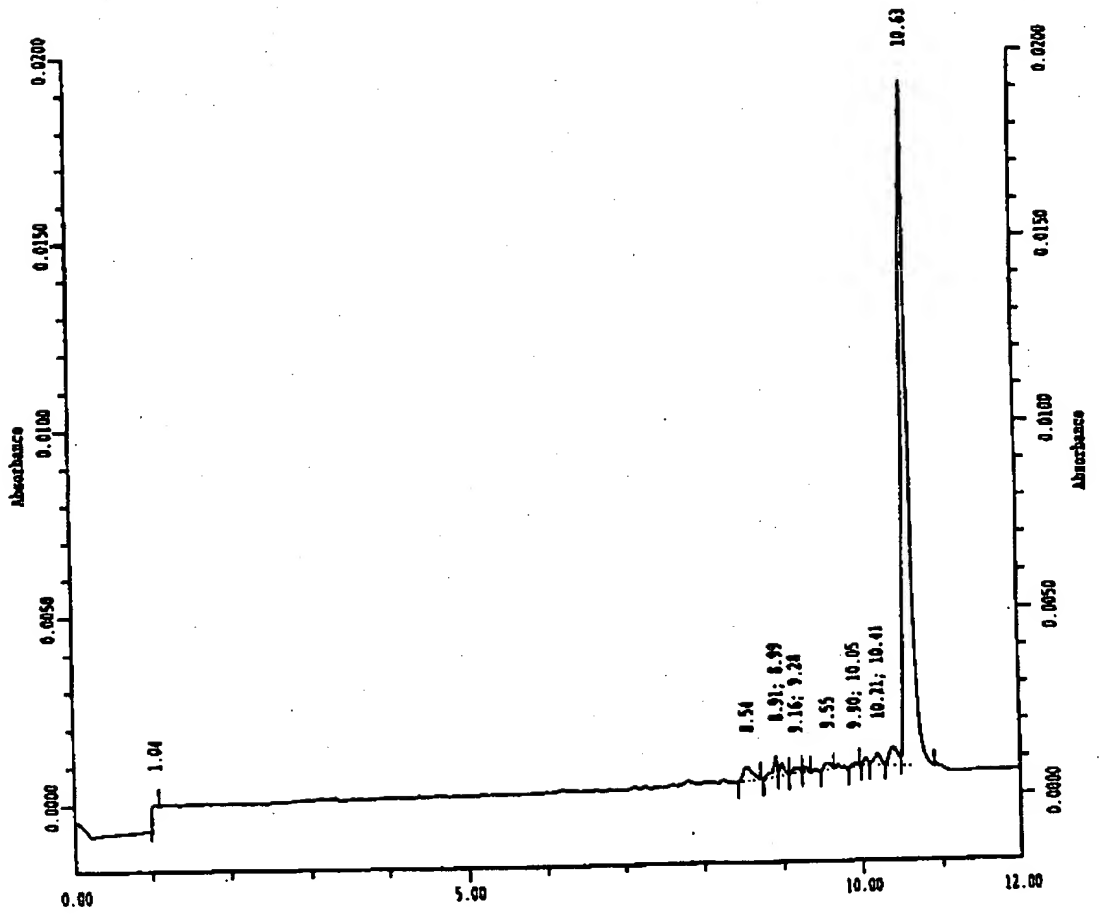
Figure 2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0.0050
0.0000
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8.54
8.91; 8.99
9.16; 9.24
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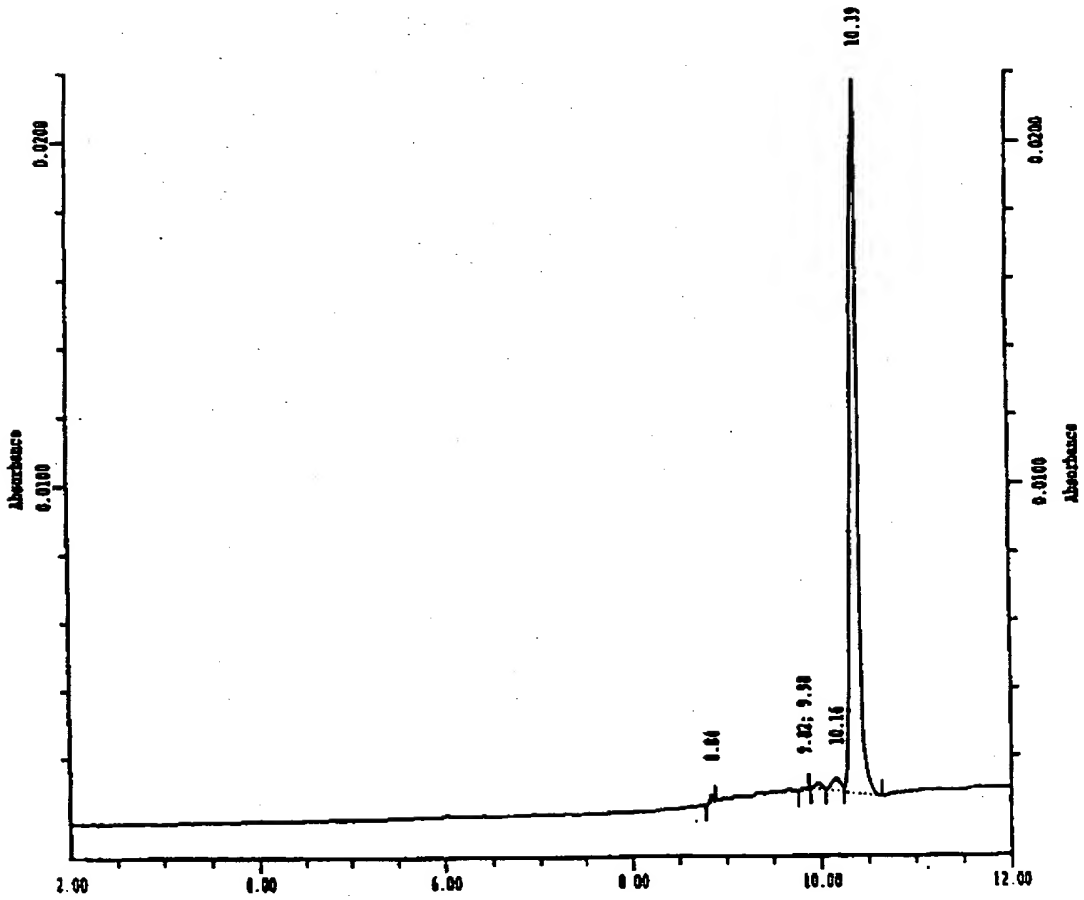
10.63
0.00
5.00
10.00
12.00

Figure 3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10.00
12.00

Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23284

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G01N 33/48; C07H 21/04
US Cl :422/104; 436/94; 536/25.4; 24.5, 24.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 422/104; 436/94; 536/25.4, 24.5, 24.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, BIOSIS, MEDLINE, DERWENT, CA
search terms: support, purify, oligonucleotides, separate, full length, deletion, elute

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	GOSS et al. High performance affinity chromatography of DNA. J. Chromatog. 1990, Vol. 508, pages 279-287, especially pages 279, 283, and 285.	88-90 ——— 1-87 and 91-95
Y	YASHIMA et al. High-performance affinity chromatography of oligonucleotides on nucleic acid analogue immobilized silica gel columns. J. Chromatog. 1992, Vol. 603, pages 111-119, especially pages 111 and 115-117.	1-95
Y	TEMSAMANI et al. Sequence identity of the n-1 product of a synthetic oligonucleotide. Nucleic Acids Res. 1995, Vol. 23, No. 11, pages 1841-1844, especially page 1841.	1-95

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 01 APRIL 1998	Date of mailing of the international search report 27 APR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KENNETH R. HORLICK Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23284

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SAIKI et al. Analysis of enzymatically amplified B-globin and HLA-DQ DNA with allele-specific oligonucleotide probes. Nature. 13 November 1986, Vol. 324, pages 163-166, especially page 163.	1-95